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THE PREPARATION AND HYDRIDE REDUCTION
OF 2-ALKOXYTETRAHYDROFURANS.

BY

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A THESIS

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The undersigned hereby certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled, The Preparation and Hydride Reduction of 2-Alkoxytetrahydrofurans. submitted by LYDIA PHINDILE MAKHUBU, in partial fulfilment of the requirements for the degree of Master of Science.

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A B S T R A C T

A series of 2-alkoxytetrahydrofurans and their 5-substituted derivatives have been synthesized.

Hydrogenolysis of the 2-alkoxytetrahydrofurans with a 1:1 molar proportion of LiAlH_4 - AlCl_3 in diethyl ether as solvent resulted in almost quantitative ring (or endo) cleavage in all cases. The greater basicity of tetrahydrofuran compared to that of dimethyl ether, diethyl ether and tetrahydropyran is used to explain the observed results. The Lewis acid will coordinate practically exclusively with the ring oxygen to give only ring cleavage products.

The group, CH_3 - at position 5 gave a preponderance of exo cleavage (exo/endo, 60/40). This could be explained in terms of the polar effect of CH_3 - in stabilizing the intermediate oxocarbonium ion. However the steric effect of this group might also have influenced the ease of attainment of the transition state leading to the oxocarbonium ion.

The group, CH_3OCH_2 -, at position 5, gave rise to endo cleavage exclusively. This again could be explained in terms of the polar effects. However since in both the 2-methoxy-5-methyltetrahydrofuran and the 2-methoxy-5-methoxymethyltetrahydrofuran, both the cis and trans isomers were not prepared, and reduced separately

it is not possible to say whether steric effects had a significant influence on the observed results.

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INTRODUCTION

It has been shown that substituents markedly affect the direction of ring cleavage of 1,3-dioxolanes by the mixed hydride reagent, $\text{LiAlH}_4\text{-AlCl}_3$ (1). These results are explained in terms of polar effects of the substituents.

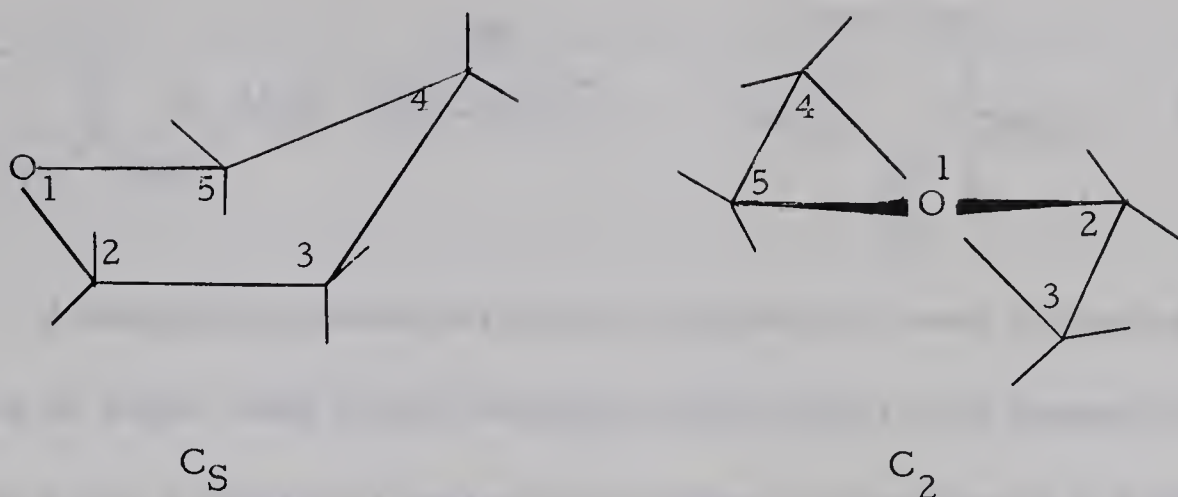
A recent publication (2) has presented some work on the hydrogenolysis of 2-alkoxytetrahydrofurans and the results of exo C-O bond cleavage versus endo C-O bond cleavage are explained in terms of steric effects rather than polar effects.

The purpose of this work was to prepare suitably substituted 2-alkoxytetrahydrofurans which could be subjected to hydrogenolysis by $\text{LiAlH}_4\text{-AlCl}_3$ to determine the influence of substituents on the extent of exo versus endo C-O bond cleavage.

LITERATURE SURVEY

The Tetrahydrofuran Ring System.

The cyclic ether tetrahydrofuran has been shown to be a non-coplanar molecule (3, 4, 5, 6). The accepted view is that the molecule is best represented by two conformations similar to those of cyclopentane (3), and designated as C_S and C_2 , or the envelope and half-chair forms respectively.

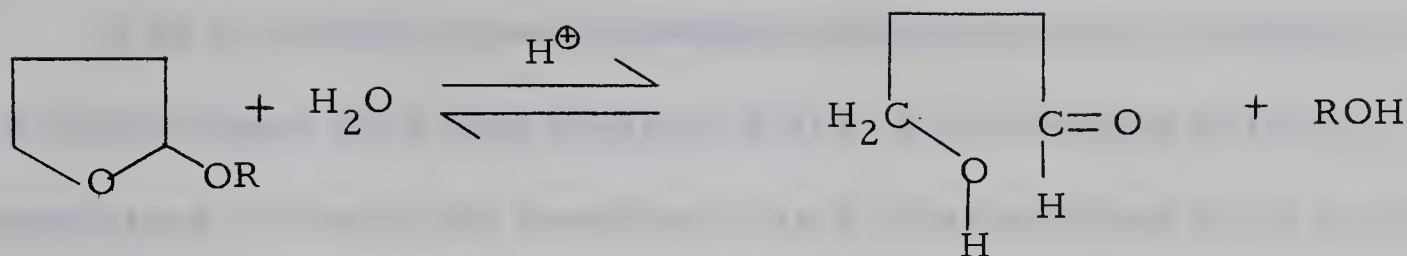


Calculations of strain energy on cyclopentane derivatives containing sp^2 hybridized atoms, such as cyclopentanone, or hetero atoms, such as tetrahydrofuran, suggest (3) that these molecules exist in the half-chair form with the maximum puckering occurring at carbon atoms 3 and 4. It has been suggested (7) that the C_S form is the most favoured conformation for the furanosides.

Tetrahydrofuran has been shown (8) to be a stronger base than tetrahydropyran. This fact has been used to explain (2) the greater ease of coordination with the Lewis acid by tetrahydrofuran than by tetrahydropyran.

Synthesis of 2-Alkoxytetrahydrofurans.

An alkoxy substituent at position 2 in the tetrahydrofuran ring system converts the structure into an acetal which can be considered to have been formed by the cyclization of a γ -hydroxyaldehyde in the presence of an alcohol in a manner analogous to the formation of furanosides in the carbohydrate field (9). Being acetals they are subject to hydrolysis as indicated by the following equation.



Although the tetrahydrofuran nucleus has been prepared by a variety of ways, only those methods which lead to the formation of 2-alkoxy-(or 2-hydroxy)-tetrahydrofurans or substituted 2-alkoxy-tetrahydrofurans will be considered here.

In an investigation of the oxymethylene lactone transformation (10) from γ -butyrolactone, the formation of several tetrahydrofuran derivatives was described. These are illustrated in Chart 1.

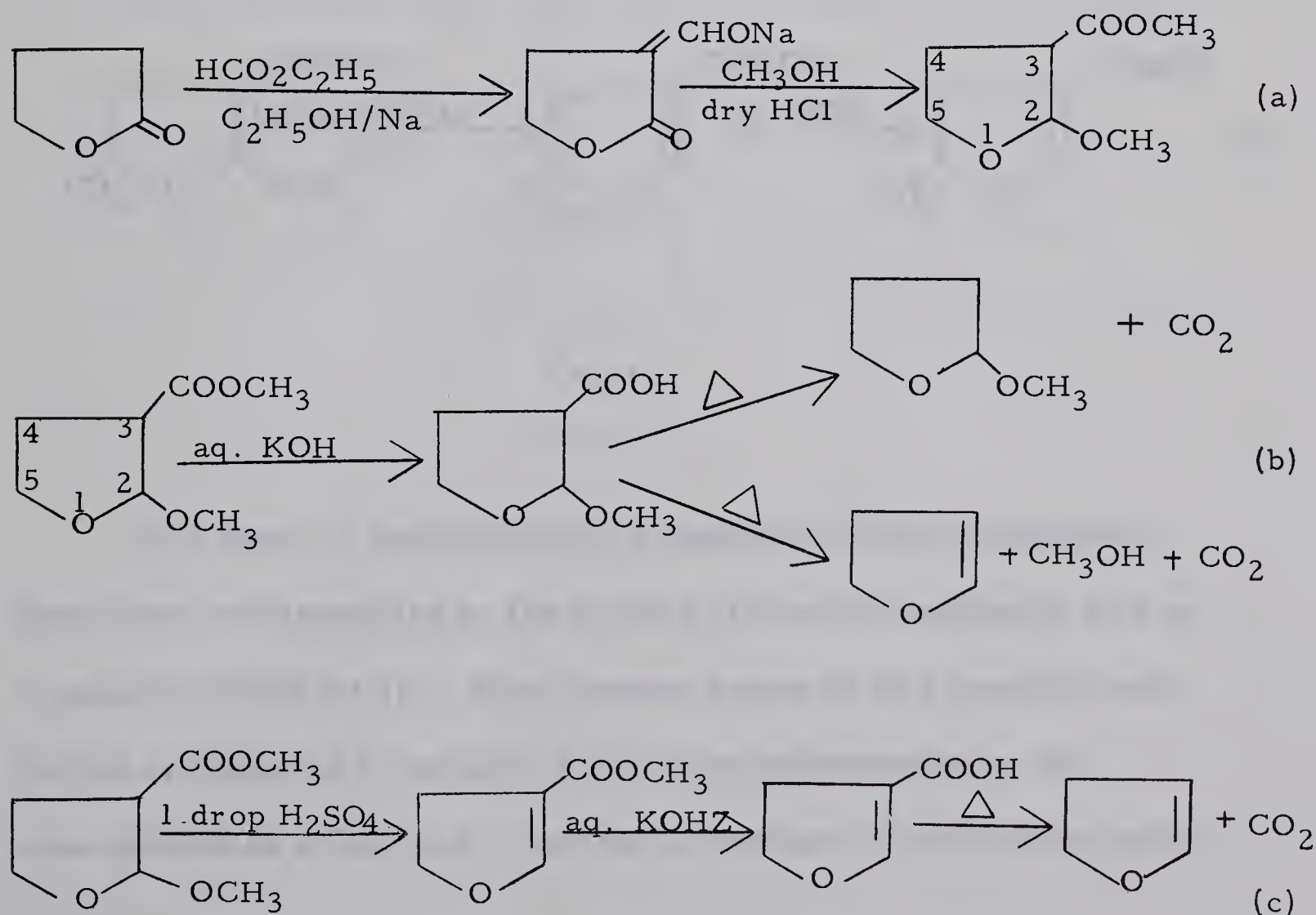


Chart 1

The 3-carboxy-2-methoxytetrahydrofuran and the 3-carboxy-4,5-dihydrofuran were both observed (10) to decarboxylate at room temperature, although the unsaturated acid decarboxylated more slowly than did the saturated acid. The reported products of the decarboxylation are those indicated by equations (b) and (c) in Chart 1.

Later (11) a similar series of transformations was performed using γ -valerolactone as the starting material (Chart 2).

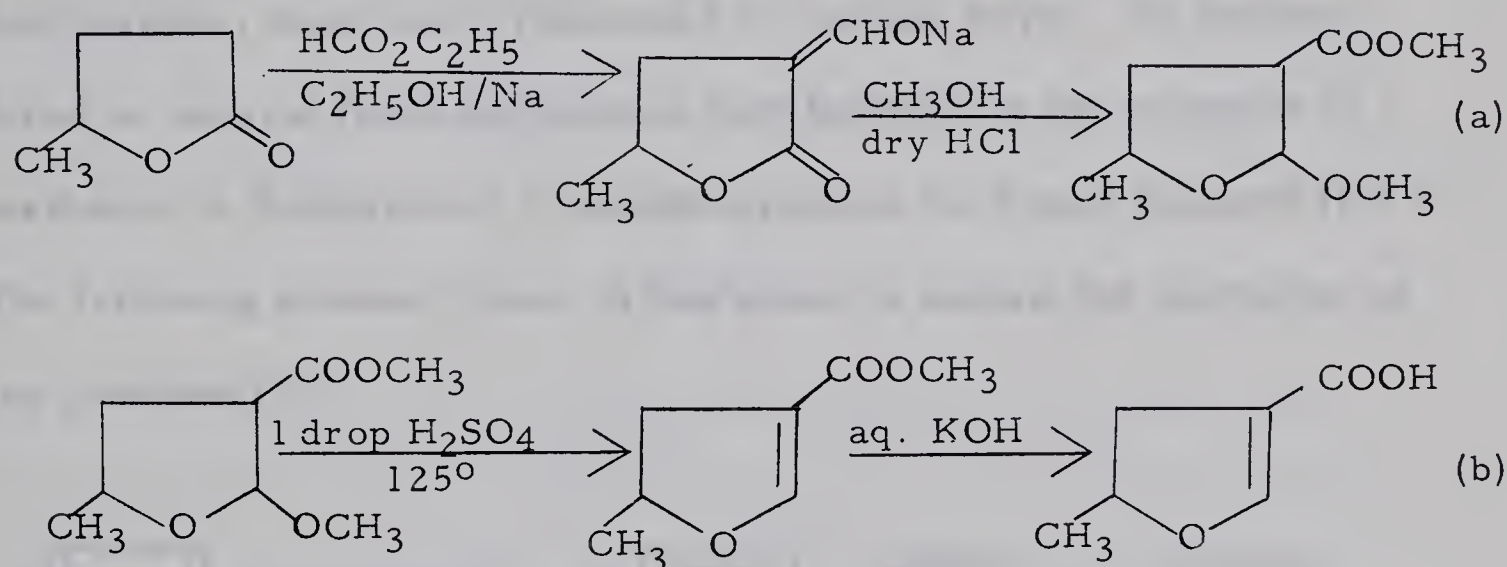


Chart 2

The ester, 3-carbomethoxy-2-methoxy-5-methyltetrahydrofuran, was not saponified by the authors (11) to the carboxylic acid as in equation (b)(Chart 1). This however seems to be a possible route for the synthesis of 2-methoxy-5-methyltetrahydrofuran by the decarboxylation of the acid 3-carboxy-2-methoxy-5-methyltetrahydrofuran.

The reaction between 2,3-dihydrofuran and an alcohol in the presence of a trace of acid is known to give 2-alkoxytetrahydrofurans in good yield (2).



2-Alkoxyfurans, which could be hydrogenated to 2-alkoxytetrahydrofurans, have been synthesized in various ways. By treating furan or several furan derivatives with bromine in the presence of methanol, 2,5-dihydro-2,5-dimethoxyfurans have been isolated (12). The following scheme (Chart 3) was given to explain the formation of the products (13).

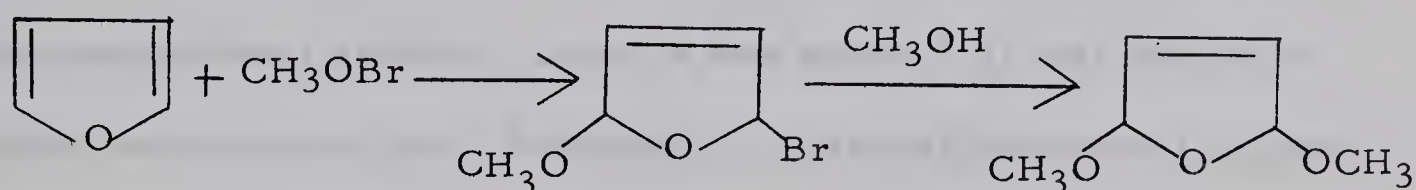


Chart 3

It was shown however (14) that the addition of bromine in methanol, to a double bond, does not necessarily involve methyl hypobromite. A possible scheme for the addition was given (14) and which may be applied to furan as shown in Chart 4.

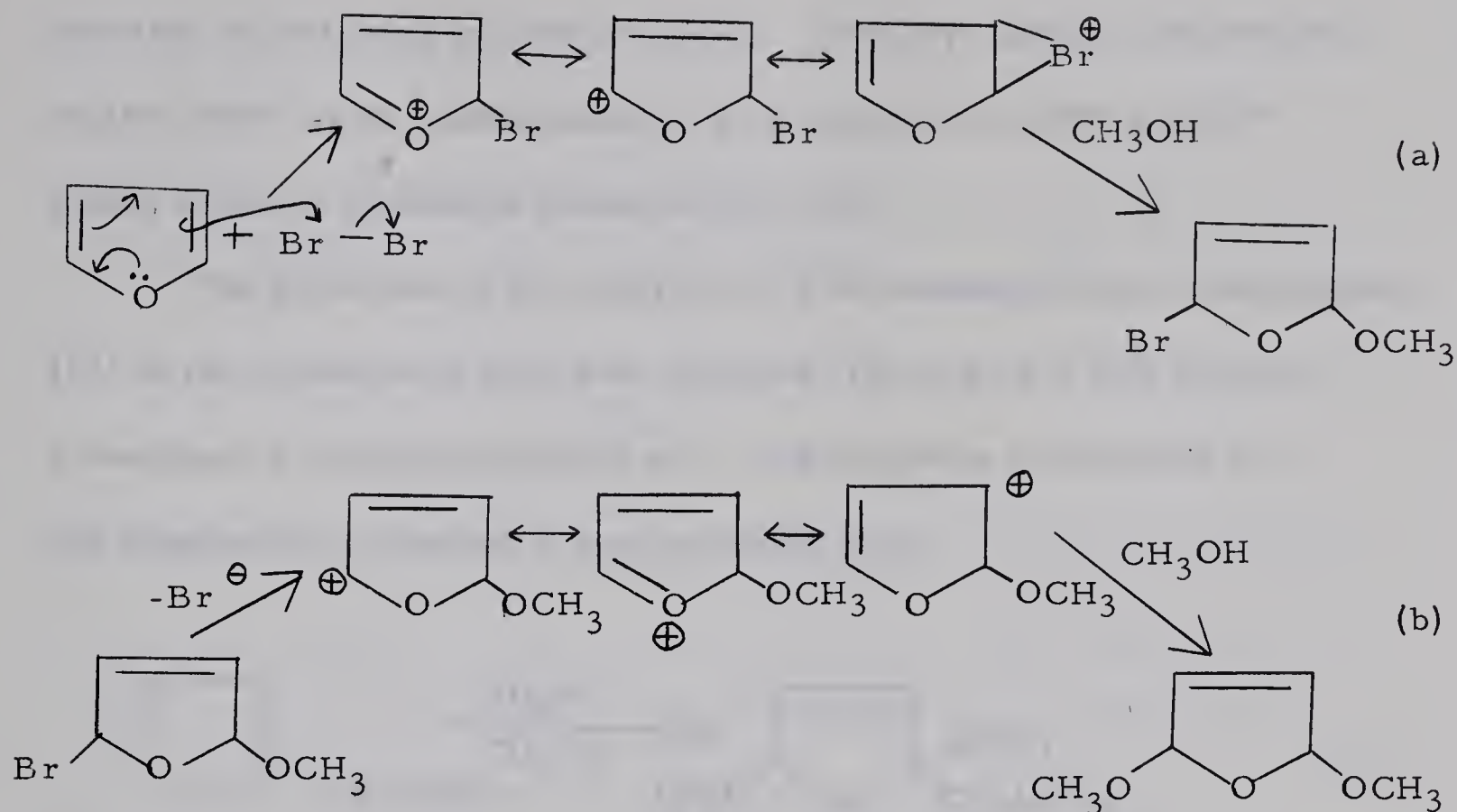


Chart 4

Furfuryl alcohol had been methoxylated in this manner by Meinel (15) who had concluded that the product was 4,5-dihydro-4,5-dimethoxyfurfuryl alcohol. Later it was shown (12) that Meinel's product was actually the 2,5-dihydro-2,5-dimethoxyfurfuryl alcohol, as indicated in Chart 5.

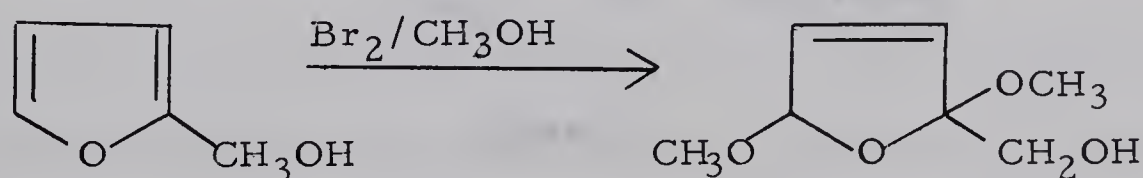


Chart 5

Later an electrolytic method for the methoxylation of furan and its derivatives was developed (16). The furan was mixed with ammonium

bromide in methanol and electrolysed. Furfuryl alcohol and furfuryl methyl ether were methoxylated to give respectively 66% and 93% yields of the 2,5-addition products (14, 18).

The pyrolysis of 2,5-dihydro-2,5-dimethoxyfurfuryl methyl ether (14) in the presence of acid was reported (19) to give a 23% yield of 2-methoxy-5-methoxymethylfuran. The following mechanism for the elimination of methanol was proposed (19).

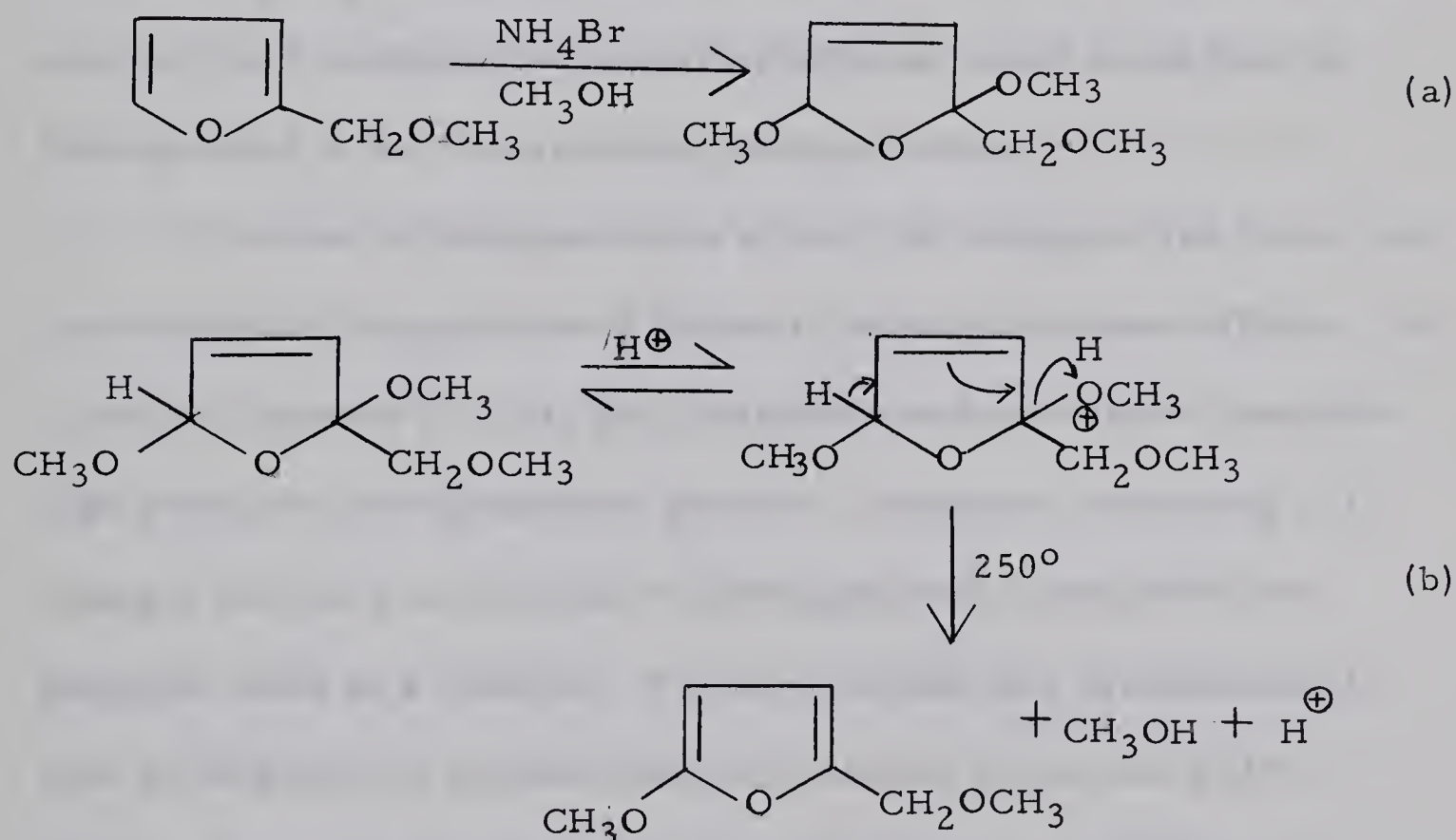


Chart 6

The final product might be hydrogenated to provide 2-methoxy-5-methoxymethyltetrahydrofuran which would be useful in our work.

The displacement of bromine from methyl 5-bromo-2-furoate with the methoxide ion has been described (20) (Chart 7).

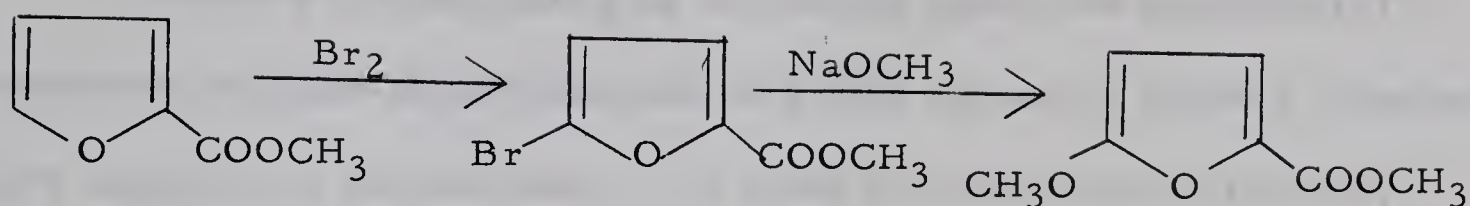


Chart 7

It was later reported that the methyl 5-methoxy-2-furoate was reduced with LiAlH_4 to give 2-methoxyfurfuryl alcohol. This might be methylated to give 2-methoxy-5-methoxymethylfuran which could then be hydrogenated to the corresponding tetrahydrofuran.

The ease of hydrogenolysis of the C-O linkage in the furan ring has rendered hydrogenation of furans to tetrahydrofurans difficult. In a series of papers (23, 24, 25), Nishimura and coworkers describe high pressure hydrogenation of aromatic compounds containing C-O linkages normally susceptible to hydrogenolysis, using rhodium-platinum oxide as a catalyst. Furfuryl alcohol was hydrogenated to give an 88% yield of tetrahydrofurfuryl alcohol in this work (23). A similar selective hydrogenation using 5% rhodium on alumina as catalyst, has been reported (26). Benzyl alcohols and benzyl ether were hydrogenated without hydrogenolysis of the C-O linkages to produce the cyclohexyl analogs in good yield, in this work. Both rhodium-platinum oxide and rhodium on alumina would be convenient catalysts in the hydrogenation of furan derivatives to their tetrahydrofuran analogs.

Reduction with $\text{LiAlH}_4\text{-AlCl}_3$

Since the use of LiAlH_4 as a reducing agent was reported (27), numerous accounts of the reduction of a wide variety of organic compounds have appeared in the literature. Its use in combination with AlCl_3 , now known as the mixed hydride reagent, was described later (28, 29). A 3:1 molar proportion of LiAlH_4 - AlCl_3 in diethyl ether could be represented by the following equation (28, 29).



A recent report (30) describes the specific reagent produced when LiAlH_4 is mixed with AlCl_3 , AlBr_3 and AlI_3 in diethyl ether. The hydroaluminum halides so produced were identified by their characteristic infrared absorption and by elemental analysis. The reactions to produce the hydroaluminum halides are summed up in the following equations (30) (Chart 9).

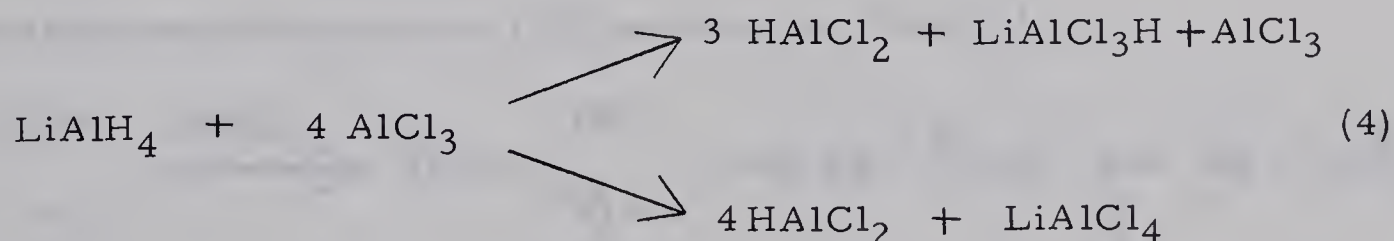
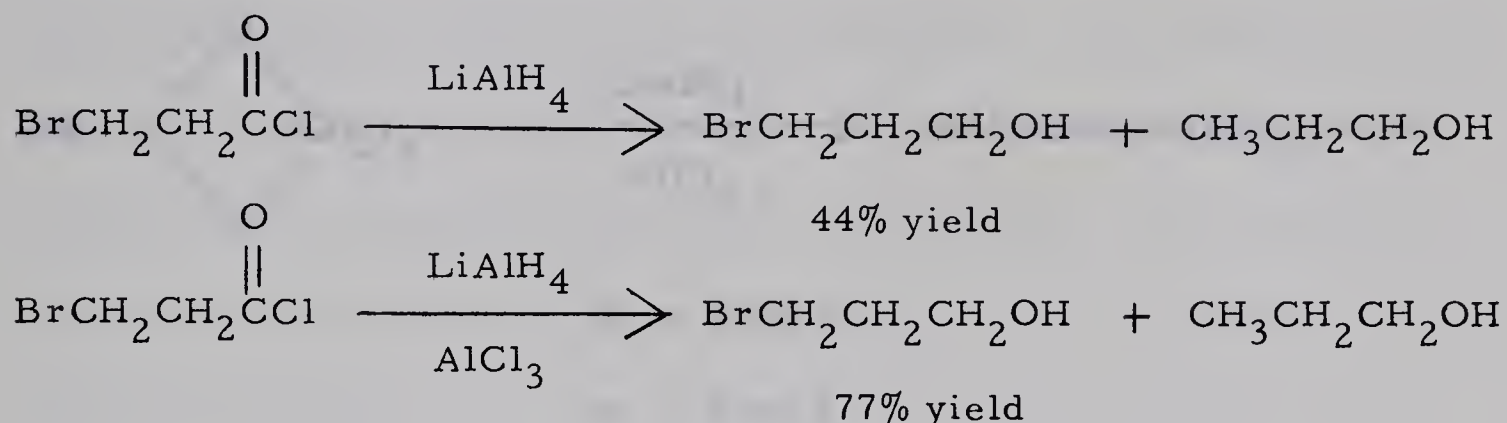


Chart 9

It was found that the LiCl produced from equations 2 and 3 when $X=Cl$, complexed with the hydroaluminum chloride in diethyl ether and hence

remained in solution.

The mixed hydride reagent was shown (31) to have greater selectivity than LiAlH_4 alone. For example



The mixed hydride has been found to reduce open chain acetals to ethers (32). It was suggested that α -chloroethers might be intermediates since they were known to lose the chlorine atom and be reduced to ethers quite readily by LiAlH_4 alone (32).

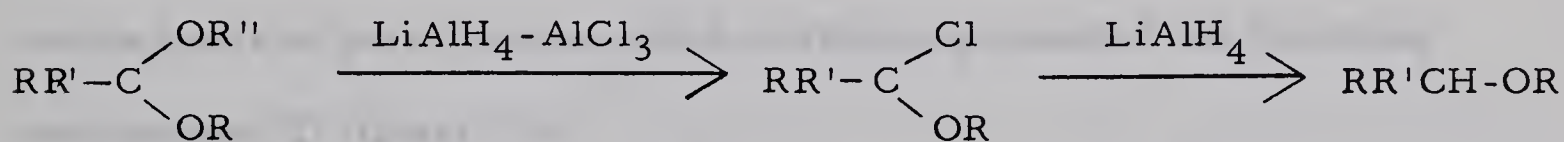


Chart 10

The same authors also suggested that the hydrogenolysis might be accomplished by a route involving a hydride attack, possibly on an intermediate oxocarbonium ion (32) as shown in Chart 11.

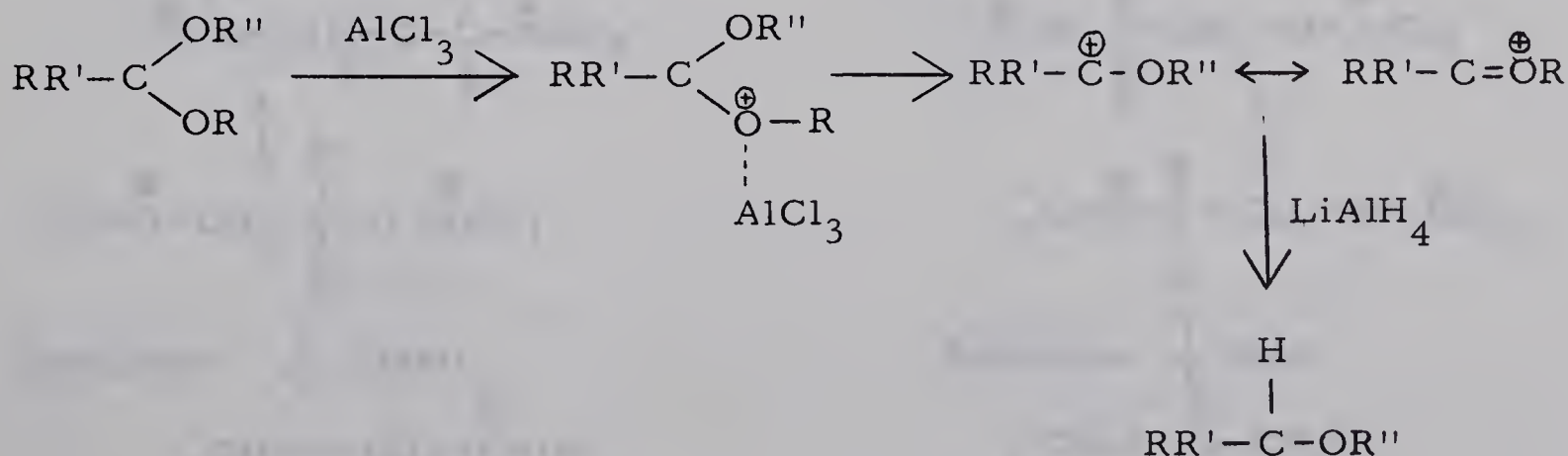


Chart 11

In a later communication (33) they reported a new synthesis of hydroxyethers and thioethers by the reduction of cyclic acetals, ketals, hemithioacetals and hemithioketals (Chart 12).

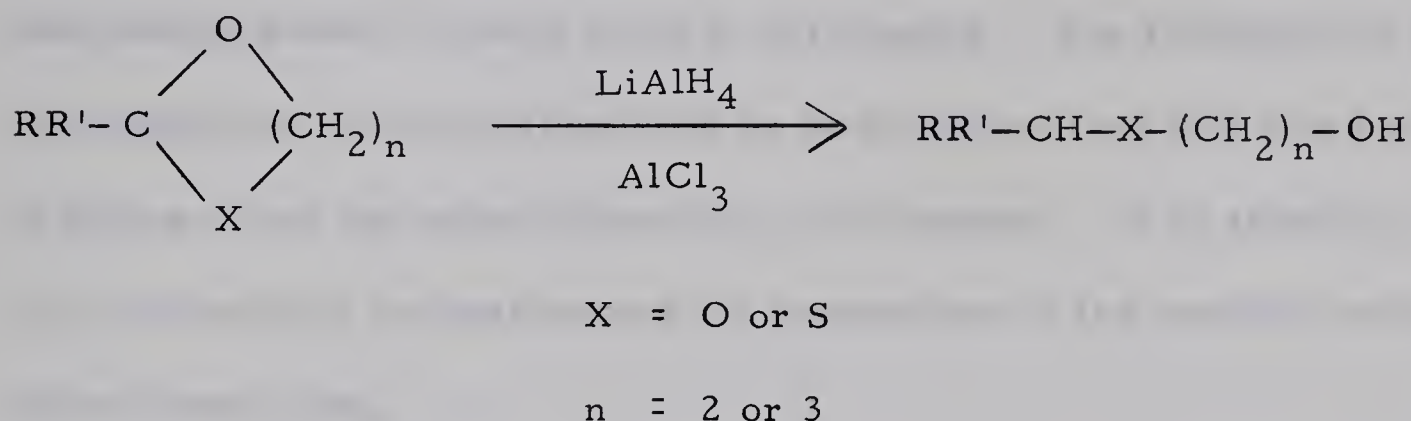


Chart 12

Leggetter and Brown (1) in a study of the cleavage of cyclic acetals and ketals, investigated the factors governing the direction and ease of ring cleavage. They showed that the results obtained could be explained on the basis of polar effects and accordingly presented the following mechanism (2) (Chart 13).

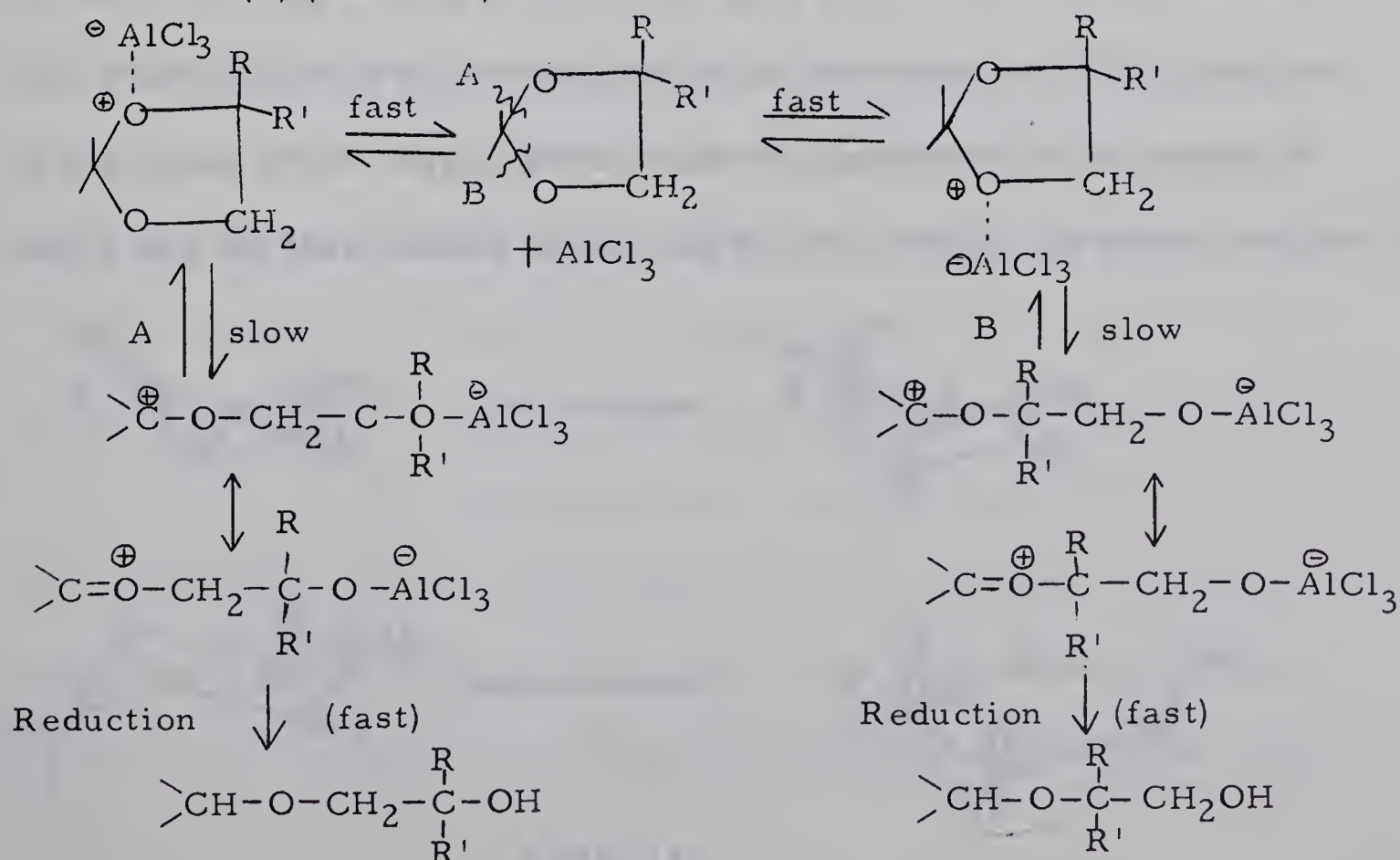


Chart 13

When R is electron-donating, route B is favored since R stabilizes the intermediate oxocarbenium ion. When R is electron-withdrawing the oxocarbenium ion obtained via route B is less stable than is the ion obtained by route A, hence route A is favoured. The formation of the oxocarbenium ion is considered to be rate-determining (34) since only in this way can the polar factors be accommodated. The stability of the intermediate ion determines the proportions of the products arising from either route.

Another factor discussed (35) is the influence of ring size on the rate of cleavage of the cyclic acetals. They reported that the 5-membered rings (1,3-dioxolanes) reduce faster than do the corresponding 6-membered rings (1,3-dioxanes). They attributed this to the greater ease of formation of the intermediate oxocarbenium ion in the 5-membered ring since this ring is more nearly coplanar initially. The stabilization of the carbonium ion by participation of the lone pair of electrons of the oxygen atom requires coplanarity of the groups R' and R and the three atoms of the ring C₂, O₃ and C₄ as shown in Chart 14.

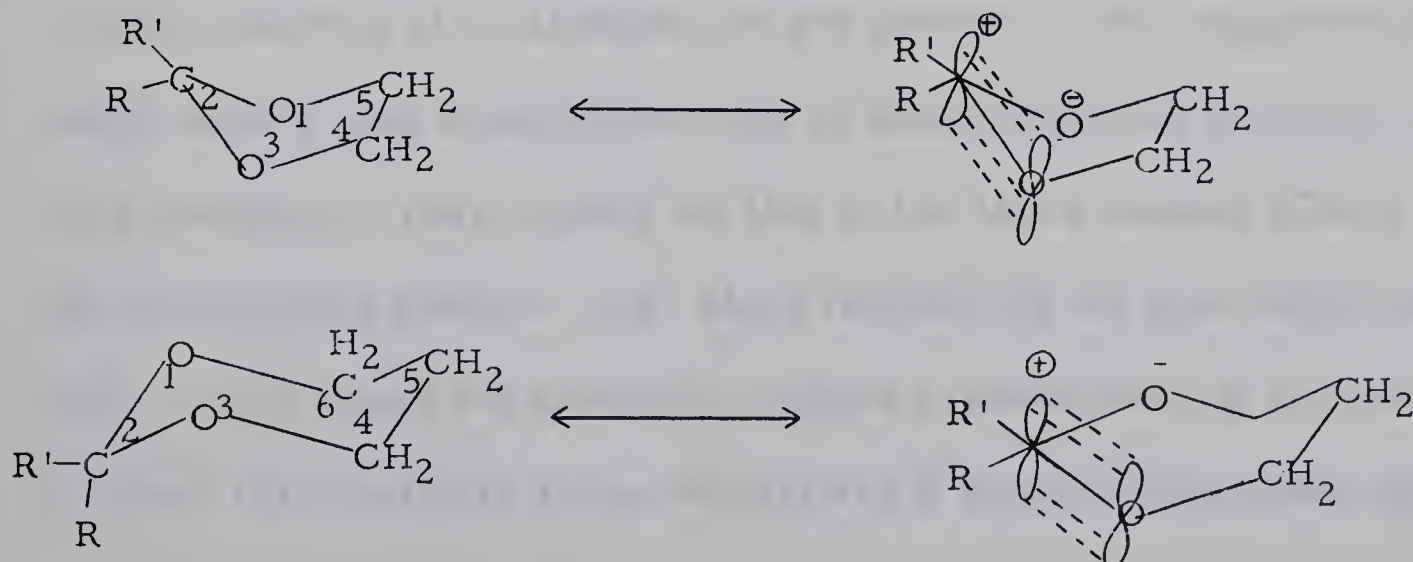


Chart 14

In the 6-membered ring this coplanarity is attained by a distortion to the half-chair form to allow overlap of the p-orbital of the O-atom with the developing empty p-orbital of the C₂ atom. The greater distortion required in the 6-membered ring makes carbonium ion formation (the rate-determining step) more difficult, hence results in a decrease in the rate of reduction.

The reduction of 2-tetrahydropyranyl and 2-tetrahydrofuranyl ethers with LiAlH₄-AlCl₃, the latter in a 1:4 molar proportion, has been reported (2) (Chart 15).

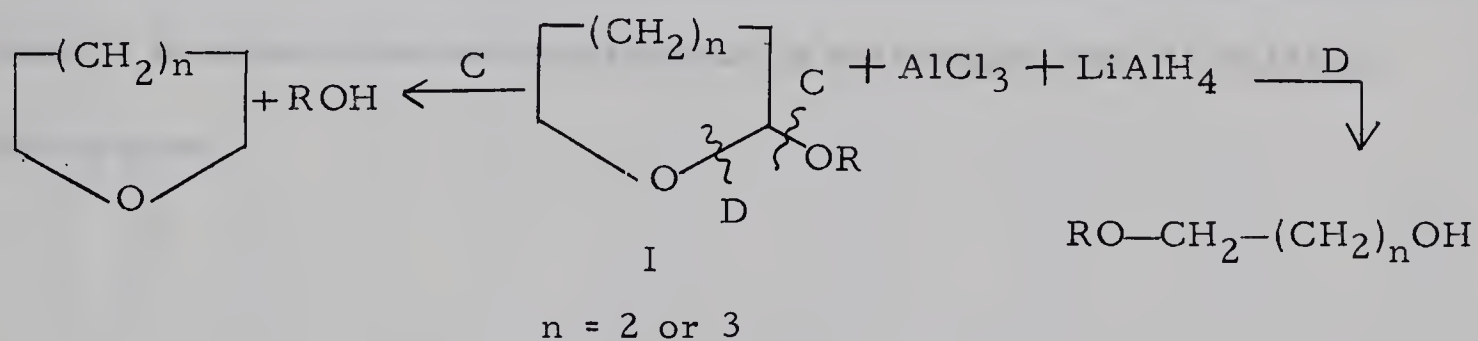


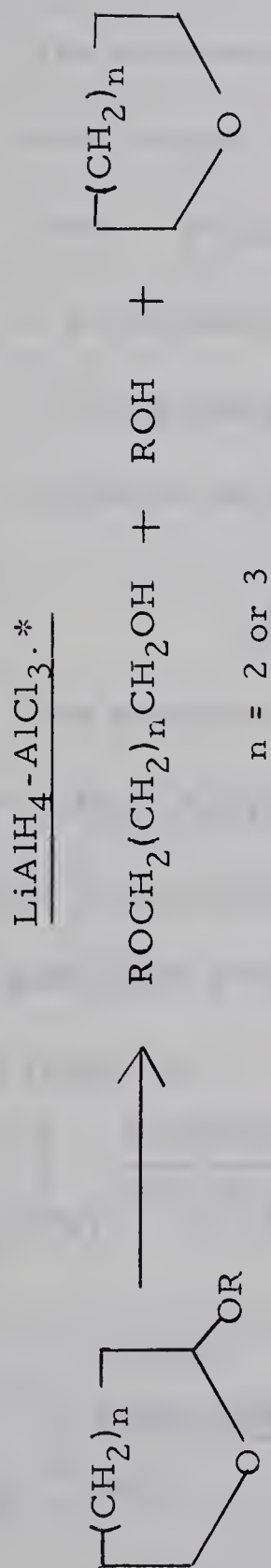
Chart 15

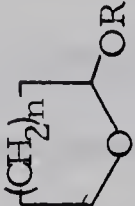
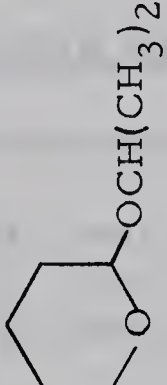
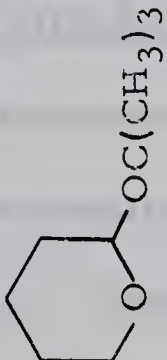
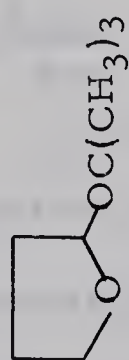
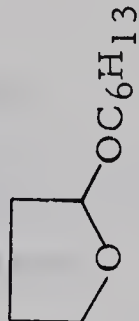
The authors (2) stated that polar effects used to explain the direction of ring cleavage of the 1,3-dioxolanes and 1,3-dioxanes described as above (1) could not account for all of the results which they obtained for the reduction of 2-alkoxyfurans and pyrans. They suggested that steric effects play a significant role in determining the direction of ring cleavage. They pointed out that in the above scheme (Chart 15), the coordinating species, e.g. AlCl₃ (actually of the type AlH₂Cl etc. (30)), would attack the endocyclic oxygen preferentially if R (Structure I, Chart 15) is tertiary since the tertiary R group would hinder approach

by the Lewis acid to the exocyclic oxygen atom of the group -OR. Hence cleavage of the ring by route D (ring cleavage) would predominate. If R were primary, it would permit no significant steric interference to the coordinating species at the exocyclic oxygen and cleavage by route C (ring retention) would predominate. Several examples taken from their work (2) are shown in Table I. They suggested that the ease of cleavage of tetrahydrofuranyl ethers, compared to the tetrahydropyranyl ethers was due to the greater ease of coordination of the Lewis acid at the tetrahydrofuranyl oxygen atom since it is known that tetrahydrofuran is a stronger base than tetrahydropyran.

TABLE I

Reduction of some 2-alkoxytetrahydrofuranyl and 2-alkoxytetrahydropyranyl ethers with



Experiment Number		% Yield of ROCH ₂ (CH ₂) _n CH ₂ OH
1		43
2		72
3		58
4		27

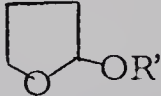
*Data taken from reference 2.

RESULTS AND DISCUSSION

The discussion of the results of the work of this thesis will be divided in two parts.

- A. The synthesis of the 2-alkoxytetrahydrofurans will be described with respect to the scope and the limitations of the methods used. Possible mechanisms will be suggested.
- B. A presentation will be made of the results of the hydrogenolysis of the acetals with $\text{LiAlH}_4\text{-AlCl}_3$ and the mechanistic interpretation of these results.

A. THE SYNTHESIS OF THE ACETALS

The synthesis of the 2-alkoxytetrahydrofurans, , with $\text{R} = \text{CH}_3\text{-}$, $\text{CH}_3\text{CH}_2\text{-}$, $(\text{CH}_3)_2\text{CH-}$, was accomplished by the sequence of reactions shown below in Chart 16. These were based on the published procedures (10, 11) referred to in the literature survey (page 3).

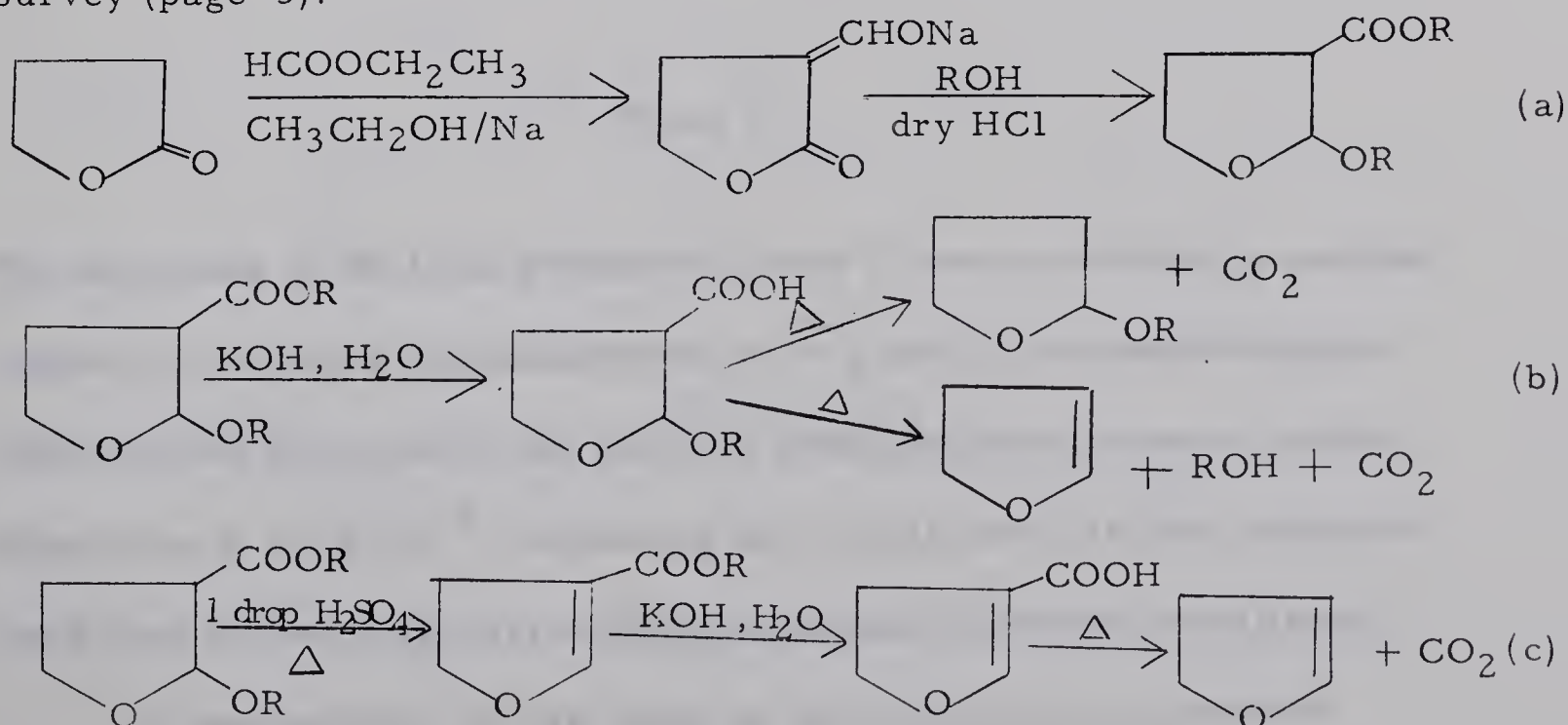


Chart 16

The yields of the ester in equation (a) were 90%, 41%, 29% for $R = \text{CH}_3-$, CH_3CH_2- , $(\text{CH}_3)_2\text{CH}-$, respectively. The decrease in the yield as R became bulkier may be attributed to the steric interference between the R groups of the C_2 -OR moiety with the substituent at position C_3 (models show this interference to be significant). The preparation of the ester (equation (a)), when $R = -\text{C}(\text{CH}_3)_3$ was unsuccessful because the ester decomposed on attempts at its purification by distillation as shown in Chart 17.

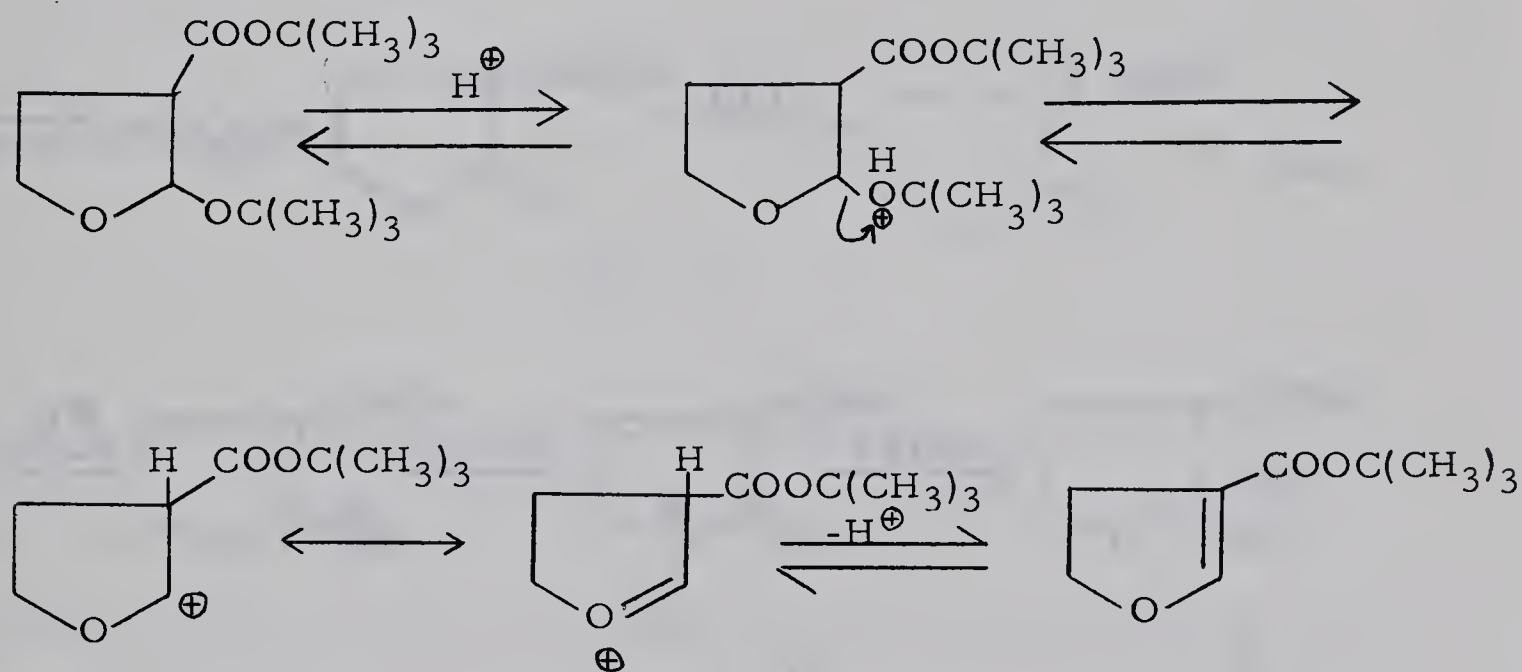


Chart 17

The structure of the final product in Chart 17 was confirmed by nuclear magnetic resonance spectroscopy (n.m.r.) and by elemental analysis. The infrared spectrum of the distilled isopropyl ester showed olefinic absorption at 1650 cm^{-1} , indicating that in this case also the molecule had begun to lose isopropyl alcohol during purification by distillation.

A mechanism, the last steps of which have been postulated

The ester is then hydrolysed to give the carboxylic acid and the acetals are formed by the decarboxylation of this acid by heat (equation (b), Chart 16).

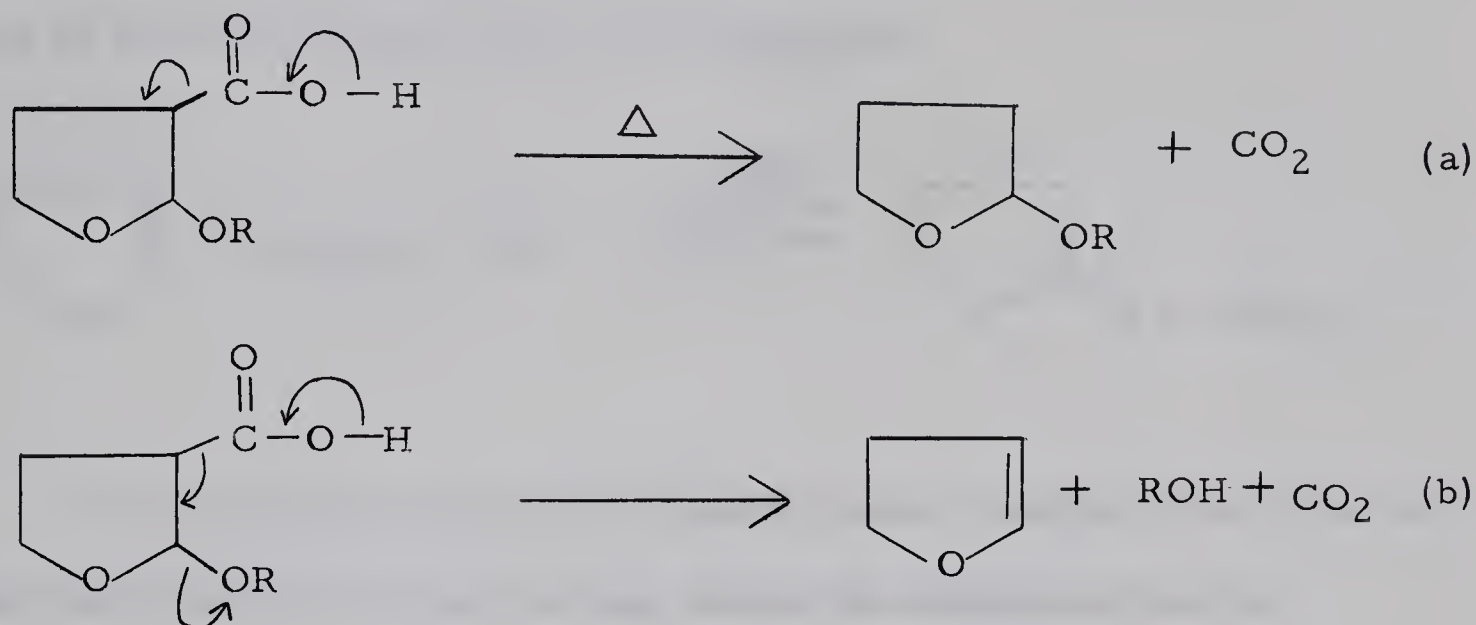


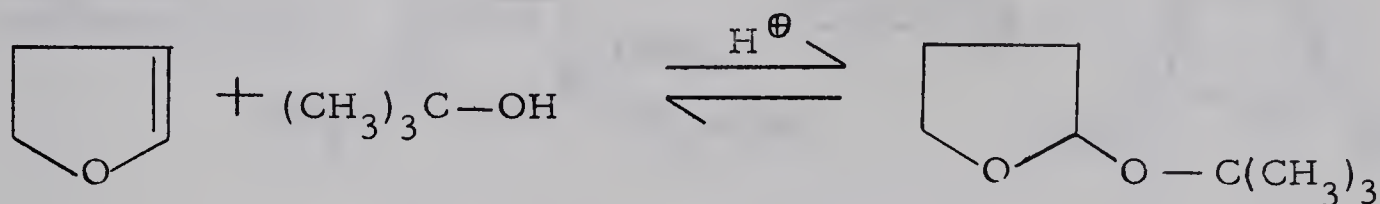
Chart 19

It was noted that the yield of the acetal (equation (a), Chart 19) decreased when the group R became bulkier. Decarboxylation with elimination of alcohol (equation (b), Chart 19) probably becomes significant when R is large since R interferes sterically with the carboxylic group at position 3.

Following equation (c) Chart 16, 2,3,-dihydrofuran was obtained in 62% yield by simply heating the free acid to its melting point without any catalyst. The decarboxylation of this unsaturated acid might occur by the same mechanism as has been advanced for the acid-catalyzed decarboxylation of cinnamic acid (36).

Although the 2-t-butoxytetrahydrofuran could not be obtained by

the reaction shown in equation (b), Chart 16, due to the rapid elimination of t-butyl alcohol, it was possible to prepare it in 60% yield by the reaction of 2,3-dihydrofuran with t-butyl alcohol in the presence of trace of acid as had been done by Eliel et al (2).



It is known that substituents appropriately located in the molecule, affect the direction of ring cleavage during the hydrogenolysis of 1,3-dioxolanes (1). Accordingly it was deemed necessary to synthesize 2-alkoxytetrahydrofurans substituted at position 5 by either an electron-donating or by an electron-withdrawing group.

The synthesis of 2-methoxy-5-methyltetrahydrofuran was accomplished by a series of steps similar to those in equations (a) and (b) (Chart 6), with CH_3 - (an electron-donor) at position 5. In this case γ -valerolactone was used as starting material.

A suitable compound possessing an electron-withdrawing group at C_5 was considered to be 2-methoxy-5-methoxymethyltetrahydrofuran. The first synthesis attempted, was based on the procedure quoted in the literature survey (12-15) and involved the following sequence of steps (Chart 20).

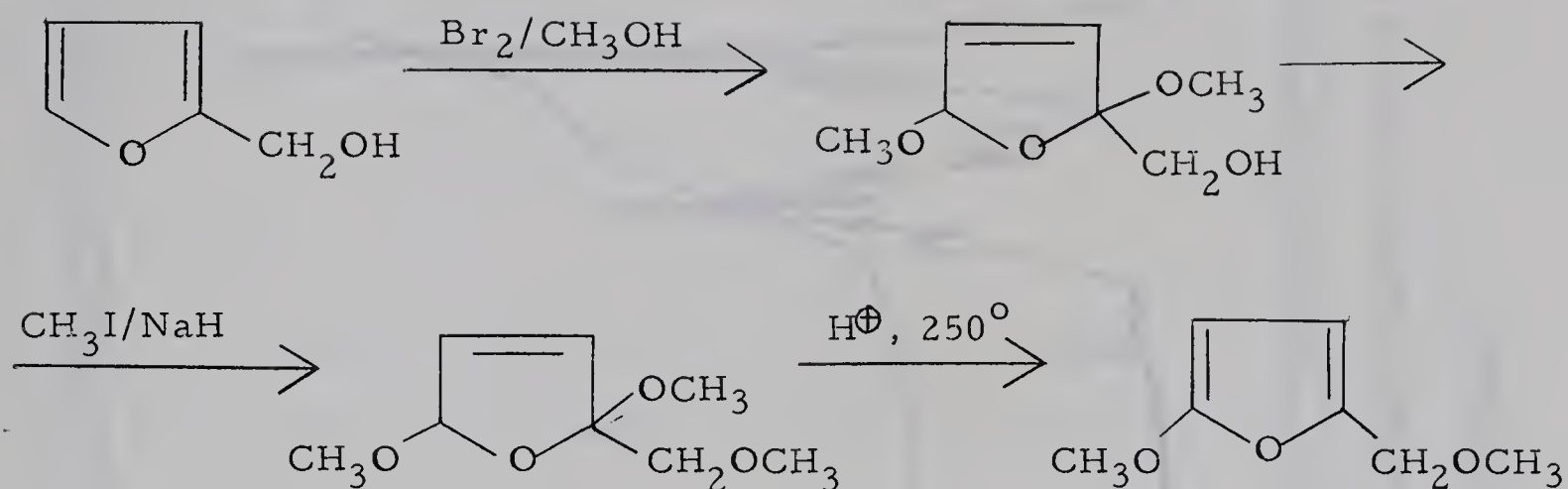
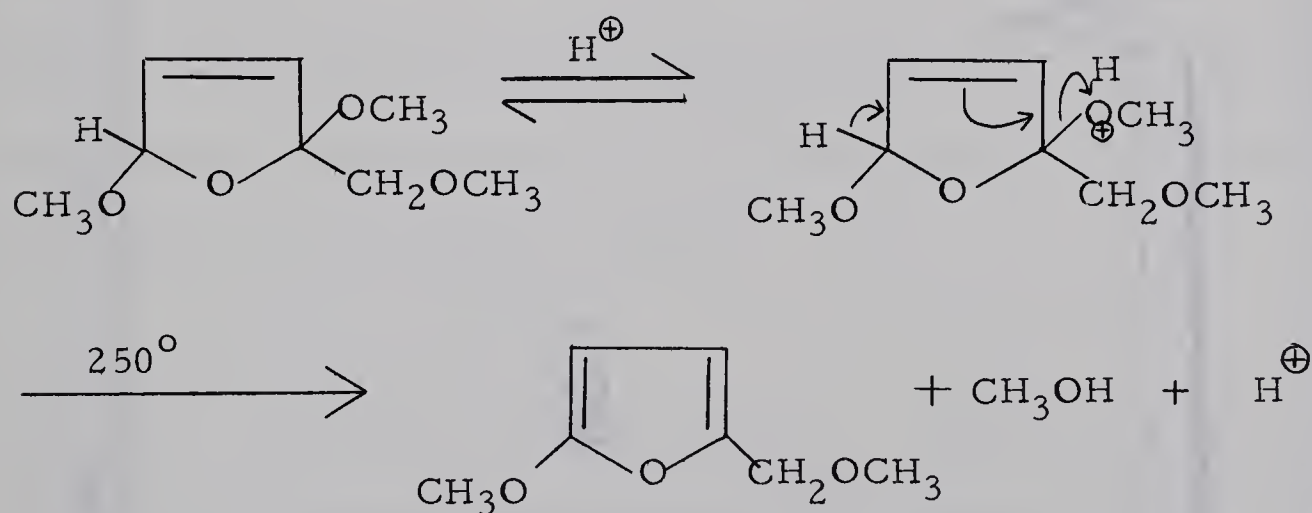


Chart 20

The mechanism for the elimination of methanol in the final step of Chart 21 has been suggested (19) to be that shown in the following equation.



In our hands, the pyrolysis at 250° , following the published procedure (19), resulted in extensive charring. The distillate collected showed 6 peaks in the gas liquid chromatogram. The major peak was collected, but its n.m.r. spectrum (Fig. 1) clearly indicated that it wasn't the 2-methoxy-5-methoxymethylfuran expected from



FIG. 1

N.M.R. spectrum of product from pyrolysis of 2,5-dimethoxyfurfuryl methyl ether at 250°.

(solvent carbon tetrachloride)

(referred to tetramethylsilane)

the overall process shown in Chart 21. The analysis data was as follows.

Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09.

Found: C, 66.86; H, 12.06.

η_D^{22} , 1.3371.

One of the minor peaks might have been the desired product but since each of these minor peaks represented a yield of about 5% and because this compound was to be subjected to further synthetic steps, the above pyrolytic method was clearly undesirable.

In an attempt to improve the procedure, the above method was modified in that the 2,5-dihydro-2,5-dimethoxyfurfuryl methyl ether was heated with stirring at 70-100° in the presence of trace of acid. Methanol distilled over. The gas liquid chromatogram of the residue showed a new peak besides that of the starting material. The new product was isolated and was shown to have the following properties.

B.p., 86° at 40 mm; η_D^{30} , 1.4575.

Anal: C, 59.08; H, 6.83.

The n.m.r. spectrum is shown in Fig. 2. Our new product obtained by heating the starting material at 70-100° as described above, was shown by n.m.r. (Fig. 2) and by comparison with an authentic sample (39) to be the dimethyl acetal of furfuraldehyde (Fig. 3). The expected product, 2-methoxy-5-methoxymethylfuran has now to be prepared by an independent method to be described later in this thesis. This product boiled at 90° at 40 mm; η_D^{26} , 1.4621. Lit. b.p., 93-100

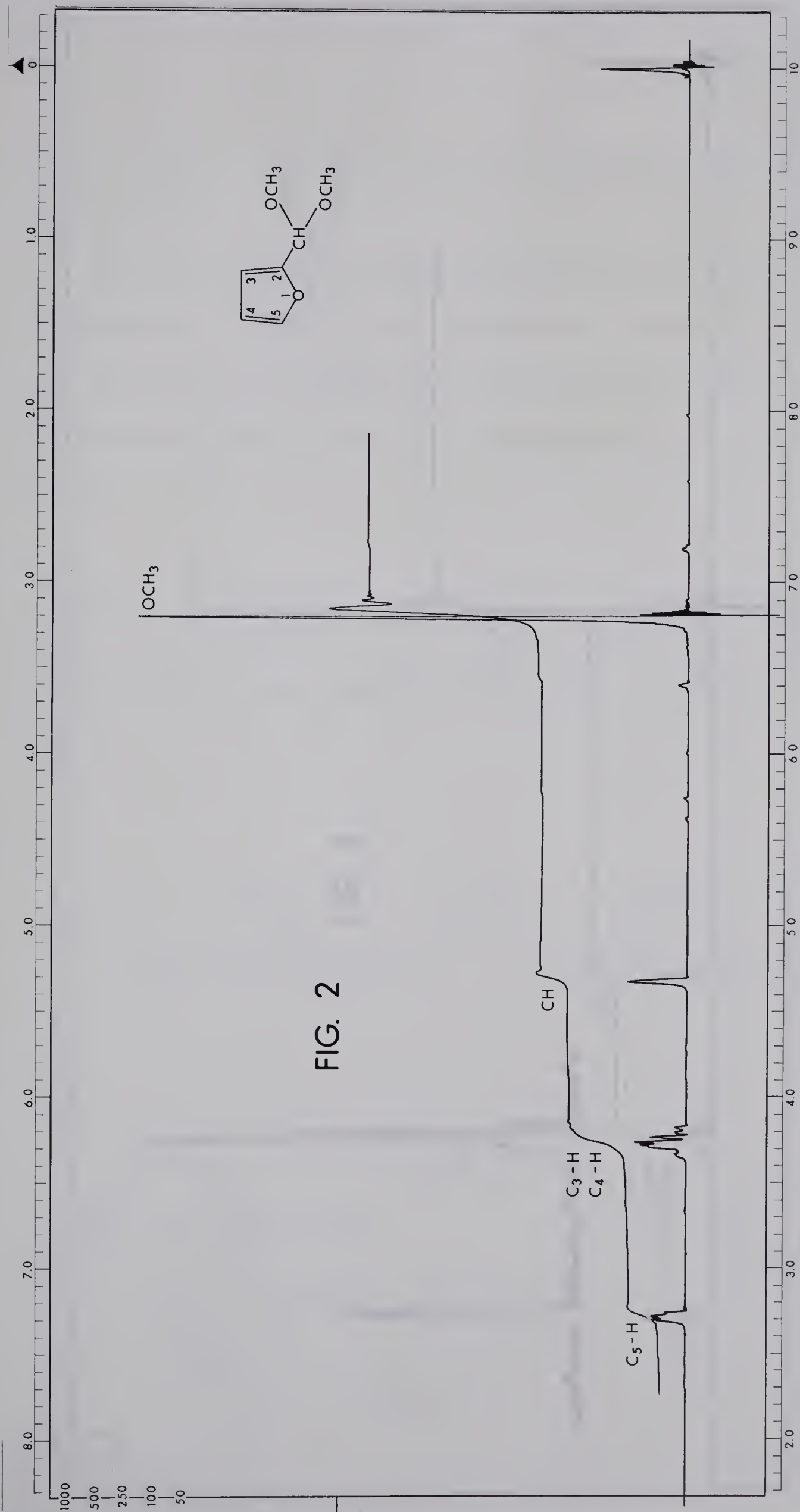


FIG. 2

N.M.R. spectrum of furfuraldehyde dimethyl acetal obtained from heating 2,5-dihydro-2,5-dimethoxyfurfuryl methyl ether at 70-100°.

(solvent carbon tetrachloride)

(referred to tetramethylsilane)

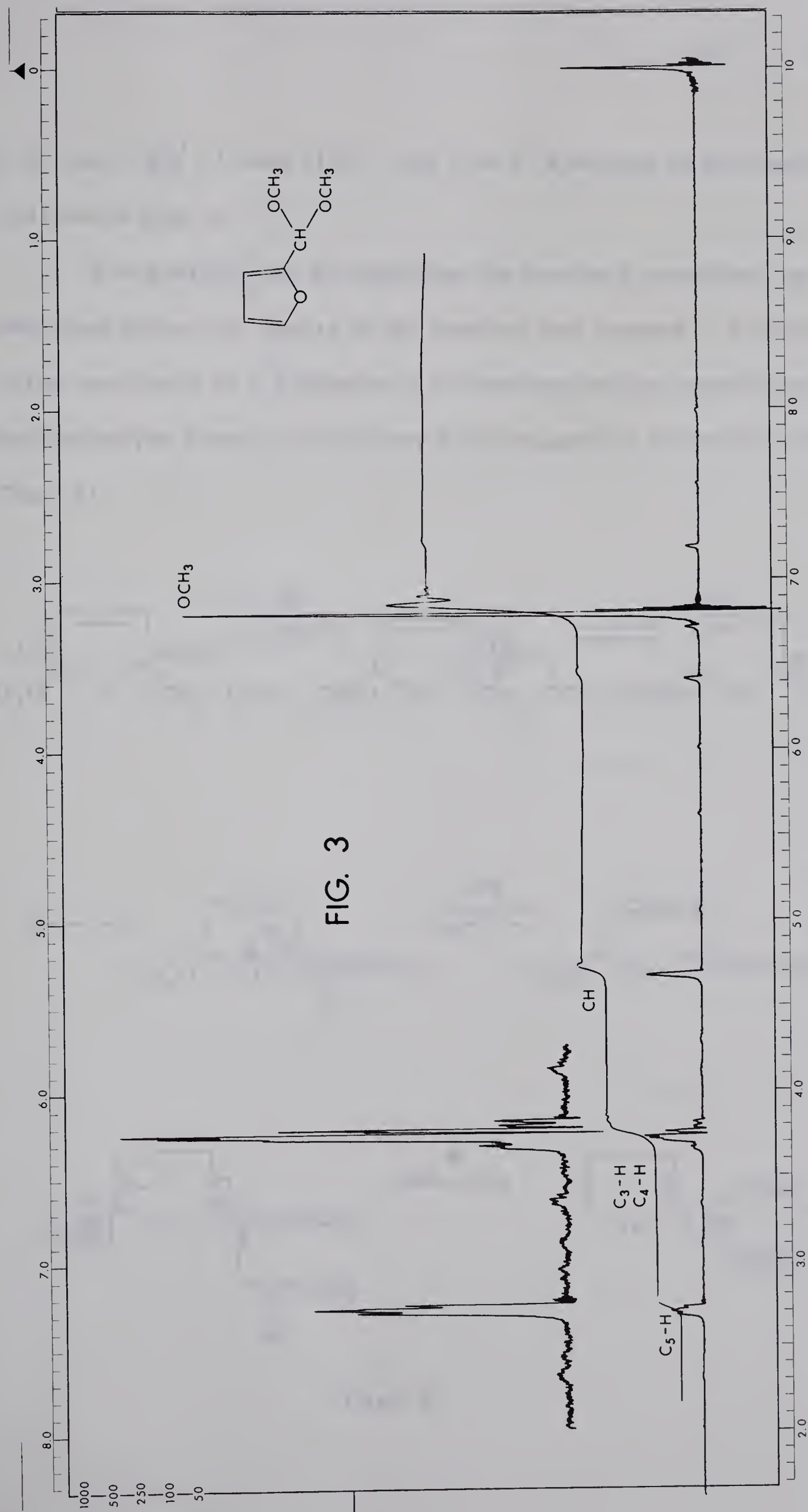


FIG. 3

N.M.R. spectrum of authentic furfuraldehyde dimethyl acetal.

(solvent carbon tetrachloride)

(referred to tetramethylsilane)

at 60 mm; n_D^{21} , 1.4620 (19). The n.m.r. spectrum of this compound is shown in Fig. 4.

It is possible that by modifying the pyrolysis procedure, as described above, the course of the reaction was changed. A mechanism of the conversion of 2,5-dihydro-2,5-dimethoxyfurfuryl methyl ether to furfuraldehyde dimethyl acetal may be formulated as shown below in Chart 21.

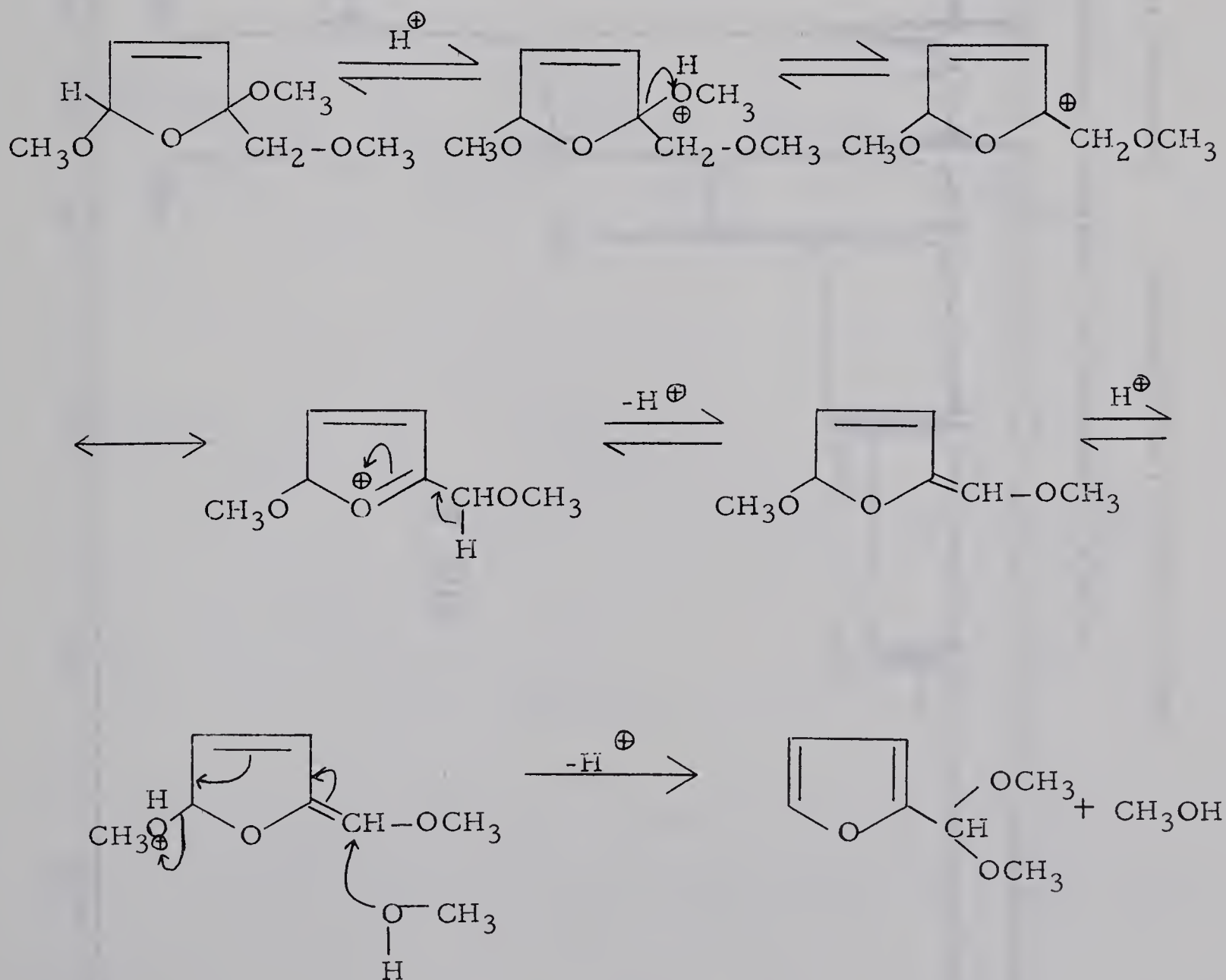


Chart 21

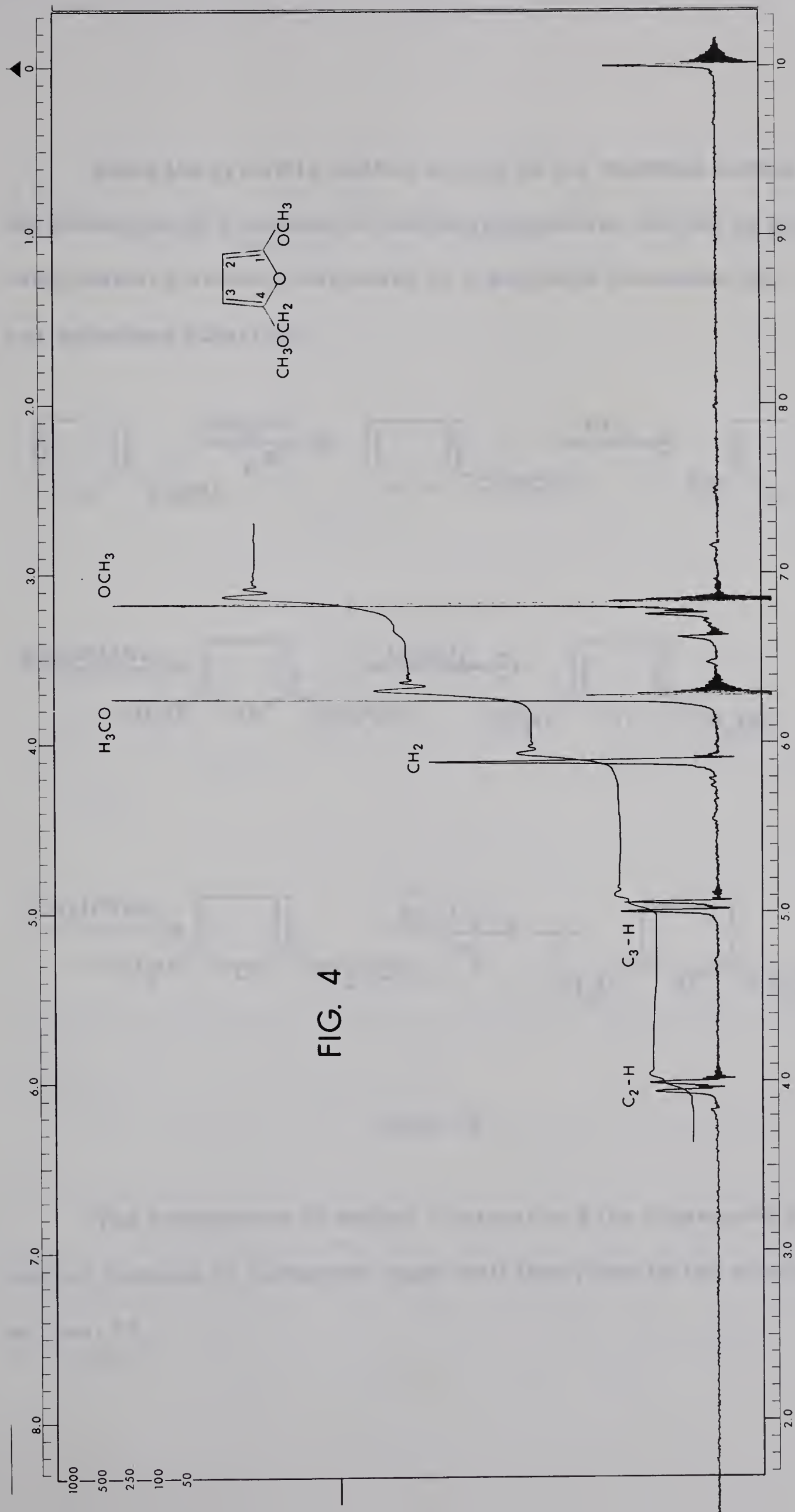


FIG. 4

N.M.R. spectrum of 2-methoxy-5-methoxymethylfuran.

(solvent carbon tetrachloride) (referred to tetramethylsilane)

Since the pyrolytic method as well as the modified method for the production of 2-methoxy-2-methoxymethylfuran has for us proven unsuccessful, a second route based on a published procedure (20, 21) was attempted (Chart 22).

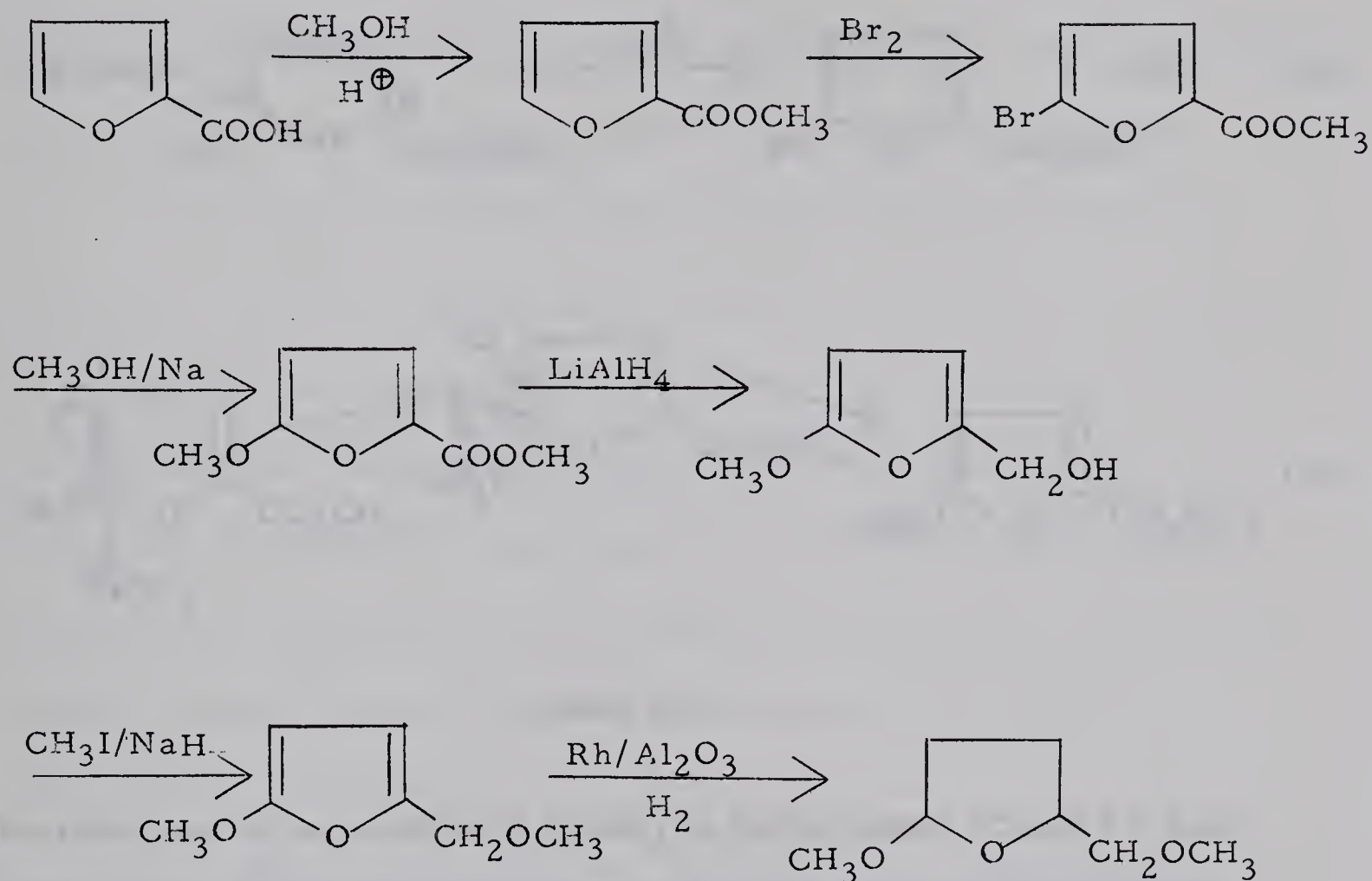


Chart 22

The bromination of methyl 2-furoate and the subsequent displacement of bromine by methoxide might well take place by the scheme shown in Chart 23.

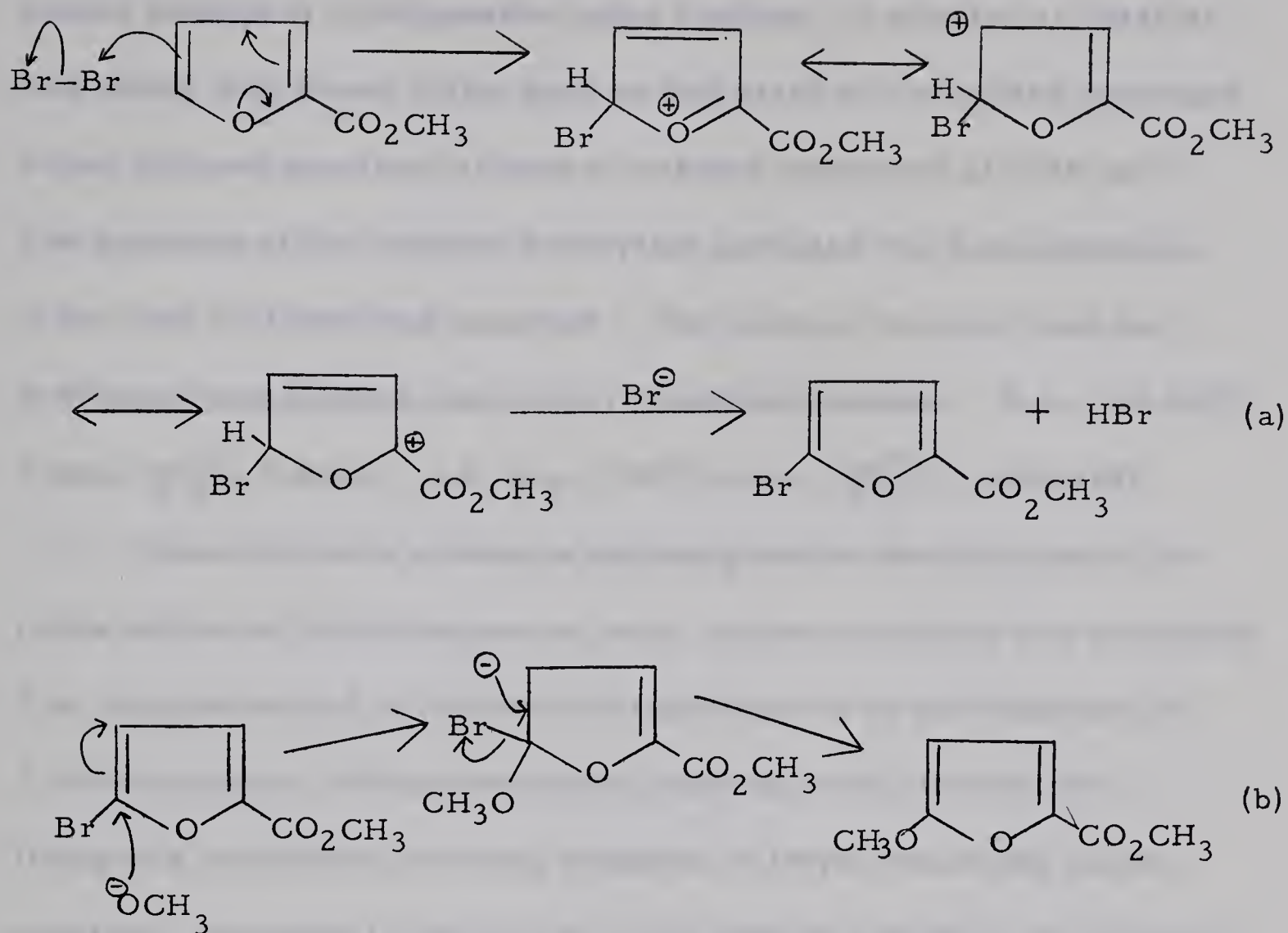


Chart 23

The reduction of the ester with LiAlH_4 in diethyl ether (Chart 23) gave a 75% yield of 5-methoxyfurfuryl alcohol which was converted readily (36) to methyl 5-methoxyfurfuryl ether.

The hydrogenation of methyl 5-methoxyfurfuryl ether was attempted at first using Raney nickel as catalyst at room temperature. However, extensive hydrogenolysis resulted giving a mixture of about seven products as shown by gas liquid chromatography. No major peak was apparent. These products were not separated and isolated. A

second attempt at hydrogenation using rhodium on alumina as catalyst (26) rather than Raney nickel gave an 84% yield of a colorless compound whose infrared spectrum showed a carbonyl absorption at 1740 cm^{-1} . The presence of the carbonyl absorption indicated that hydrogenolysis of the ring C-O bond had occurred. The product obtained from the hydrogenolysis mixture was methyl 5-methoxyvalerate. B.p., $63-65^{\circ}/9\text{ mm}$; n_D^{23} , 1.4160. Lit. b.p., $70^{\circ}/11\text{ mm}$; n_D^{20} , 1.4150 (48).

Since the above synthesis had not given the desired product due to the failure of the hydrogenation step, another synthesis was attempted. The preparation of 2,3-dihydroxytetrahydropyran by the treatment of 2,3-dihydropyran with peroxybenzoic acid has been reported (41). Using this method the following sequence of steps, employing known reactions, was used to prepare the final product 2-methoxy-5-methoxymethyltetrahydrofuran starting with 2,3-dihydro-2-hydroxymethyl-4 H -pyran (Chart 24).

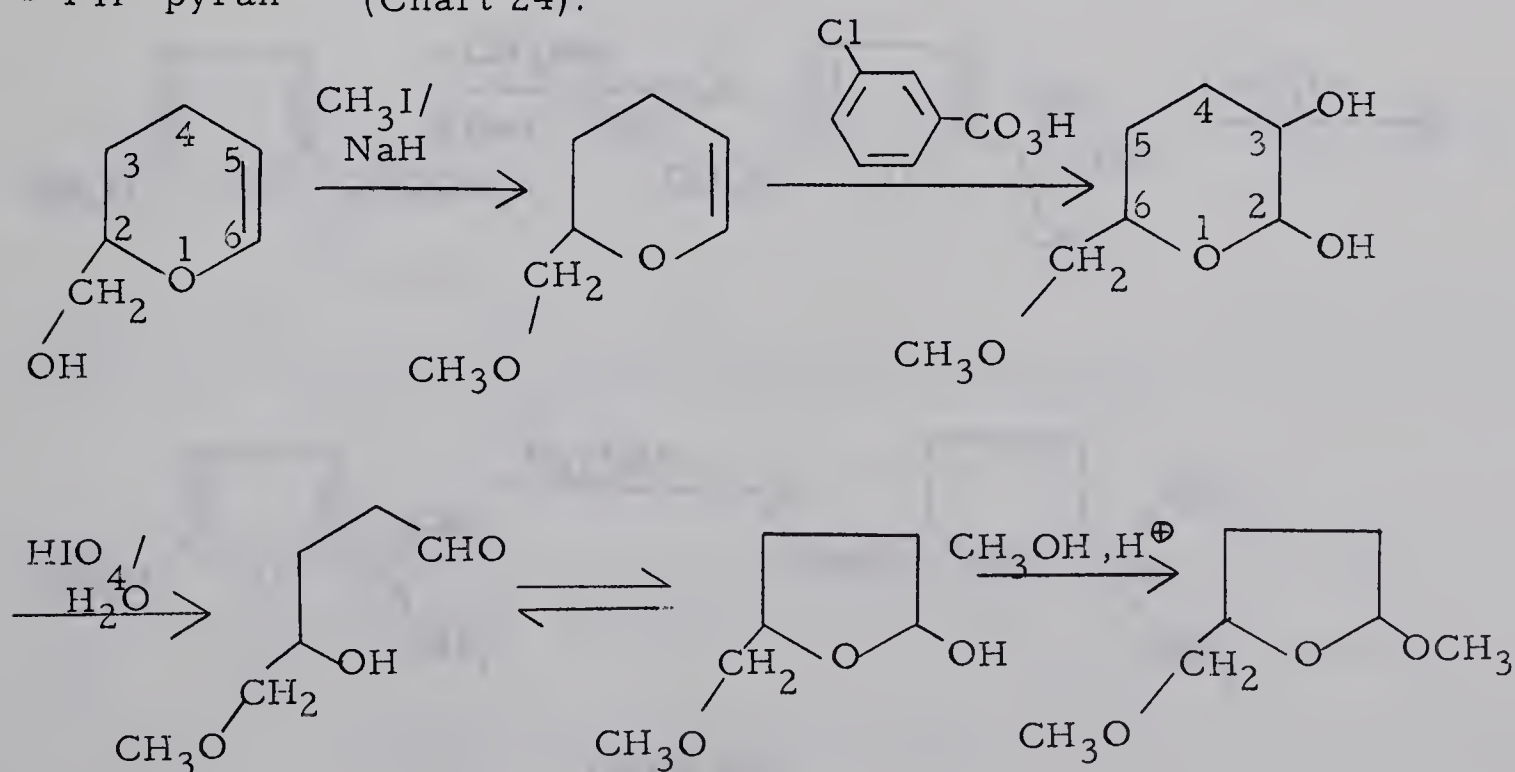


Chart 24

The 2,3-dihydroxy-6-methoxymethyltetrahydropyran was not purified since distillation might have led to dehydration. Attempts at distilling the equilibrium mixture of the aldehyde and the tetrahydrofuran resulted in the formation of unsaturated material as indicated by the infrared spectrum of the distillate (absorption at 1650 cm^{-1}). The remainder of the crude mixture was therefore treated with methanol in the presence of a trace of concentrated hydrochloric acid. This provided a 73% yield of 2-methoxy-5-methoxymethyltetrahydrofuran, based on the crude equilibrium mixture.

Several attempts were made to synthesize a 2-alkoxytetrahydrofuran with a bulky group, the isopropyl group, at position 5. The first attempt (Chart 25) was based on a published procedure which worked very well with methyl 2-furoate as starting material (22). We required methyl 5-methoxy-2-furoate as initial material.

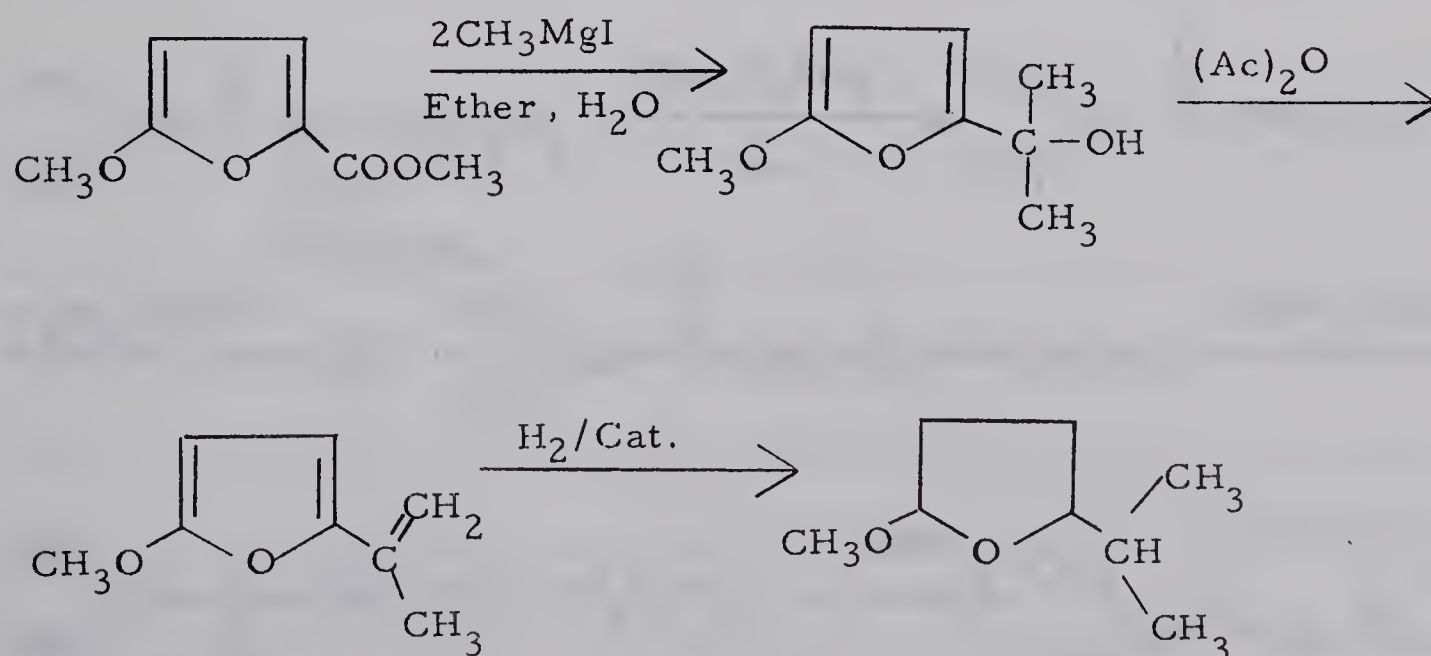
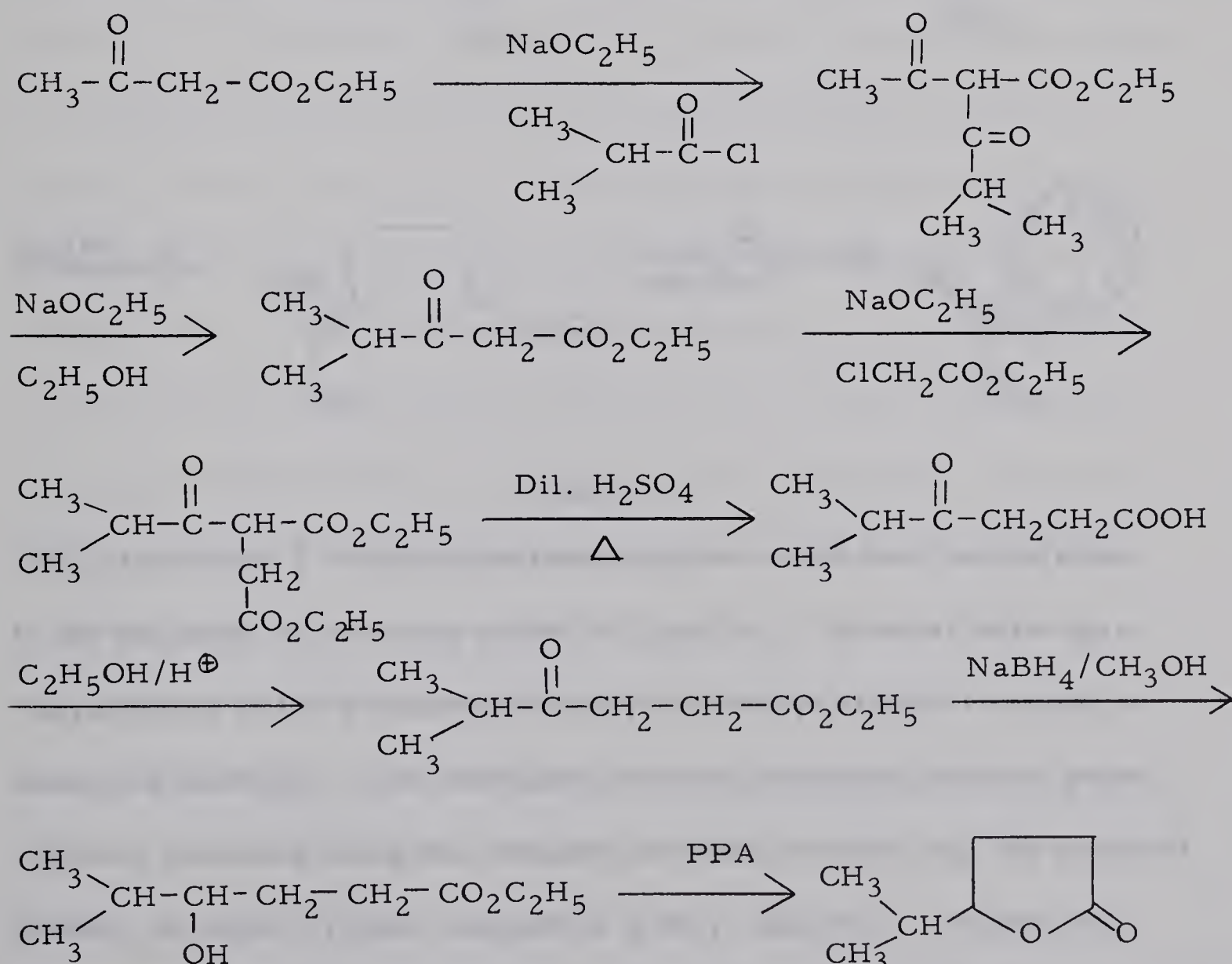


Chart 25

Steam distillation after the first step of the sequence of reactions gave a mixture and attempts at purification by distillation resulted in charring. The n.m.r. spectra of the fractions collected during the distillation did not show the vinyl protons of the furan ring.

The second procedure involved first an attempt at the synthesis of γ -isopropyl- γ -butyrolactone by a modification of a combination of published procedures (42) (Chart 26). The lactone might then be subjected to the procedure already described (10) for the synthesis of the 2-alkoxytetrahydrofurans shown in Chart 16.



(PPA = polyphosphoric acid)

Chart 26

The hydroxyester in the final step was not isolated since distillation might have led to dehydration. Cyclization of the hydroxyester did not give the lactone as indicated by the n.m.r. spectrum and the elemental analysis of the cyclized product.

The third attempt was based on a procedure described in the literature by Colonge and Girantet (43). Chart 27.

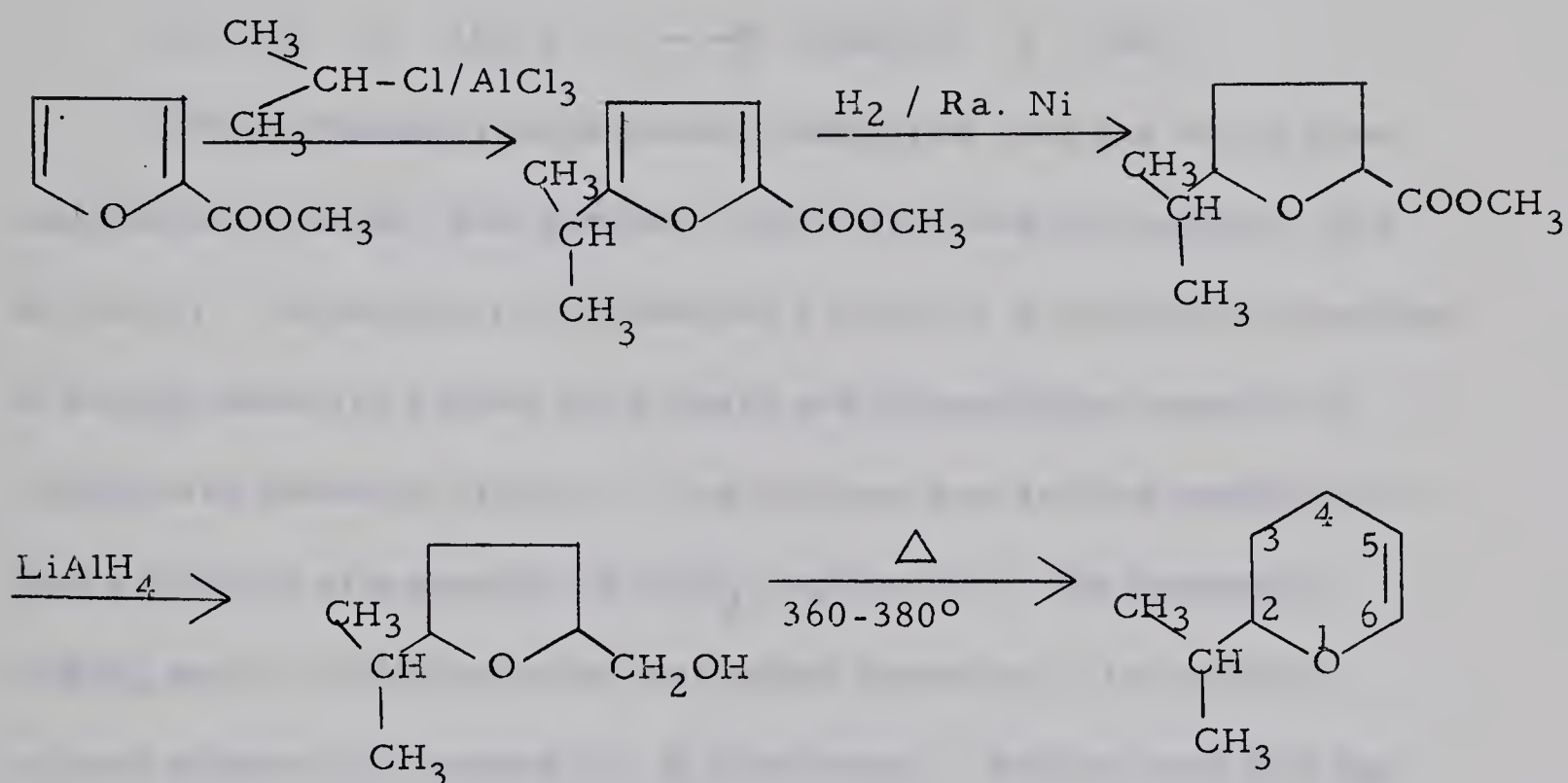
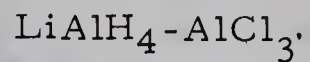


Chart 27

The 2-isopropyl-2,3-dihydro-2H-pyran would then be subjected to the sequence of reactions shown in Chart 24. However here again the pyrolysis of the 5-isopropyltetrahydrofurfuryl alcohol resulted in extensive charring. The distillate collected consisted of three peaks. All were collected using the Autoprep but none of these was the expected product as shown by their respective n.m.r. spectra. To date the synthesis of the 5-isopropyl-2-alkoxytetrahydrofuran has not been successful.

B. REDUCTION OF THE 2-ALKOXYTETRAHYDROFURANS WITH

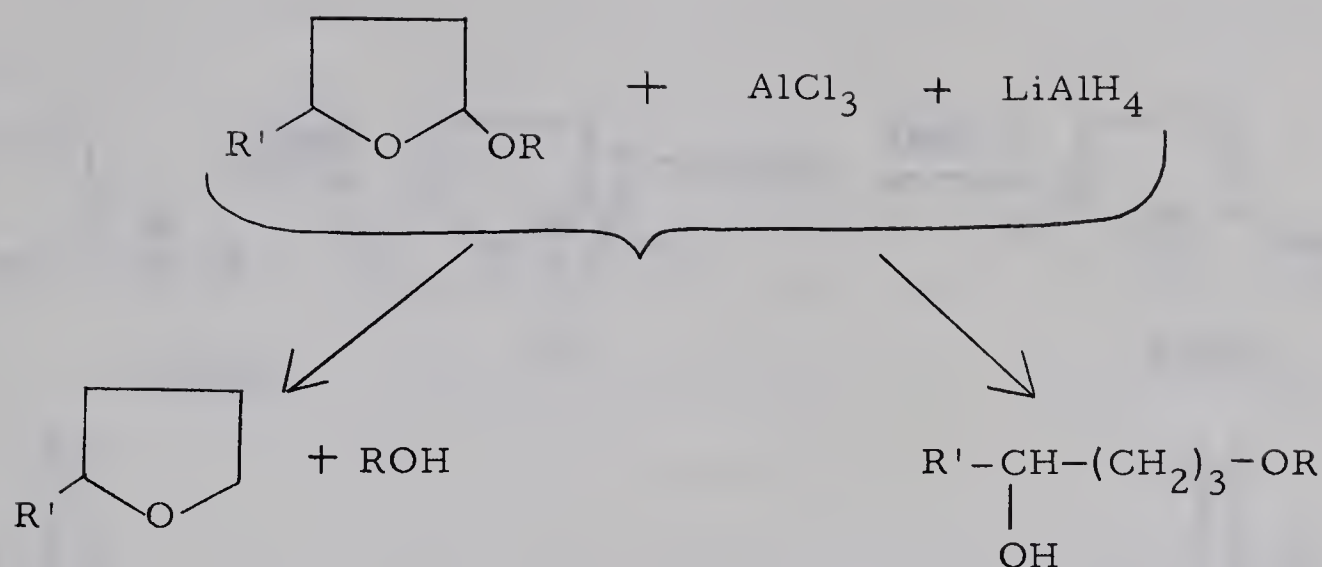


The 2-alkoxytetrahydrofurans were hydrogenolysed using a 1:1 molar proportion of $\text{LiAlH}_4\text{-AlCl}_3$ in diethyl ether as solvent. It has been shown that a mixture of LiAlH_4 and AlCl_3 in a molar ratio of 1:1 in diethyl ether produces the reducing species AlH_2Cl (30).



The hydrogenolysis procedure employed, and one which gave satisfactory results, was similar to that described by Leggetter and Brown (1). According to this method a quantity of acetal was dissolved in diethyl ether (in a three neck flask) and an equimolar amount of LiAlH_4 was added all at once. The mixture was stirred rapidly and then a solution of a quantity of AlCl_3 , equimolar to the amount of LiAlH_4 above, in diethyl ether was added dropwise to the rapidly stirred mixture in a period of ≤ 15 minutes. Recent work (40) has shown that with the addition of the first third of the AlCl_3 , the species AlH_3 is produced, which is then converted to AlClH_2 as more AlCl_3 is added. But if the time of addition of AlCl_3 is short the active reducing species under the conditions employed is AlH_2Cl .

The hydrogenolysis of the acetals is expected to give either endocyclic or exocyclic products as shown in Chart 28.



1. $\text{R} = -\text{CH}_3, -\text{C}_2\text{H}_5, \textit{i}\text{-C}_3\text{H}_7, -\text{C}(\text{CH}_3)_3$

2. $\text{R}' = -\text{CH}_3, -\text{CH}_2\text{OCH}_3$

Chart 28

Since the reduction products were obtained by a non-reversible process and also were found to be stable under the reaction conditions, a quantitative estimation of these products would provide a measure of the preferred route (i. e. relative rate) of reaction.

At this point a mechanistic route for the reductive cleavage of 2-alkoxytetrahydrofurans might be written based on that formulated by Leggeter and Brown for the hydrogenolysis of 1,3-dioxolanes and 1,3-dioxanes (1). Such a scheme is shown in Chart 29.

If polar effects are dominant here in determining the route of the reaction, as indicated by Leggeter and Brown for the 1,3-dioxolanes (1), then the relative stabilizing effect of the alkyl groups R and R' should dictate which ion will be formed in preference and hence which route of reduction should predominate.

The hydrogenolysis of 2-alkoxytetrahydrofurans possessing the substituent R as $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, $i\text{-C}_3\text{H}_7$ or $-\text{C}(\text{CH}_3)_3$ and R' as H, $-\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$ should throw some light on this question.

During the course of this work a report appeared describing the reductive cleavage of 2-alkoxytetrahydrofurans (2). To explain the results obtained the authors stated that although polar effects no doubt played a part, steric factors were considered to have a significant if not dominant role in determining the course of reaction. Some of the results are assembled in Table II for ease of comparison.

They found that when R was a tertiary alkyl group, a larger proportion of ring cleavage occurred than when R was primary (Table II). This could be explained in terms of polar factors. However they stated that steric factors could also explain the results. They suggested that when R is tertiary, route B (Chart 29) predominates largely because the bulky R group interferes with the approach of the coordinating species to the exocyclic oxygen. When R is primary the coordinating species can attack the exocyclic oxygen and route A (Chart 30) predominates.

The results of our work on the hydrogenolysis of a series of 2-alkoxytetrahydrofurans, in which the alkyl group is changed from primary to tertiary are shown in Table III.

The results in Table III indicate that regardless of the size of the alkyl groups, and their structure as primary or tertiary, ring

TABLE II

Reduction of 2-alkoxytetrahydrofurans with $\text{LiAlH}_4\text{-AlCl}_3^*$



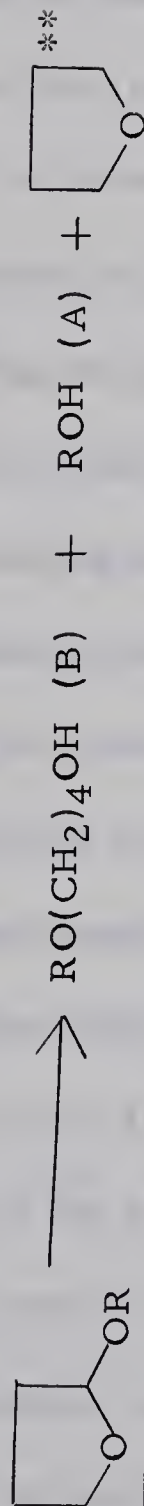
Experiment	R	Yield, % B
1	$(\text{CH}_3)_3\text{C}$	58
2	cyclohexyl	63
3	$\text{n-C}_6\text{H}_{13}$	27
4	$\text{C}_6\text{H}_5\text{CH}_2$	4

*Data taken from reference 2.

TABLE III

The Reduction of 2-alkoxytetrahydrofurans with $\text{LiAlH}_4\text{-AlCl}_3$:

(diethyl ether as solvent; at room temperature)



Experiment Numbers	R	% Yield* of $\text{RO}(\text{CH}_2)_4\text{OH}$ (B)
1	CH_3	86
2	CH_2CH_3	82
3	$\text{CH}(\text{CH}_3)_2$	80
4	$\text{C}(\text{CH}_3)_3$	86

* Refers to % yield of hydroxyether after distillation, based on the starting acetal.

** Only traces of alcohol and tetrahydrofuran showed in the g.l.c.. Total recovery was not calculated on the basis that the amount of alcohol and tetrahydrofuran was not estimable by g.l.c..

cleavage (route B, Chart 29) predominates nearly exclusively. Tetrahydrofuran and the corresponding alcohol, the products of exo bond cleavage (route A), were found to be present only in trace amounts as indicated by gas liquid chromatography of the reduction mixture. The yield of the ring cleavage product was excellent in all cases ($\geq 80\%$). The values reported in Table III were actual yields of isolated pure material based on the starting acetal. Considering inevitable losses accompanying such purification, the true yield of the ring cleavage product is no doubt well above 90%.

According to Eliel (2), since the methyl group is much smaller than the t-butyl group (Expts. 1 and 4, Table III), the former should hydrogenolyse considerably if not largely by route A (ring retention) and the latter by route B (ring cleavage). But it is clear from our work that both acetals hydrogenolyse essentially via ring cleavage. It appears, from Table III, that steric effects of the alkyl groups attached to the exo oxygen do not offer a significant influence in the direction of cleavage of the acetals.

The results of Leggetter and Brown (1) for the hydrogenolysis of 1,3-dioxolanes supports their view that the inductive effects of substituents dictate the direction of ring cleavage. Using the approach adopted by Diner (44), if one writes the 4-methyl-1,3-dioxolane as shown below in Chart 30 and imagines a division as shown by the dotted line, one clearly sees that the carbonium ion a is stabilized by the

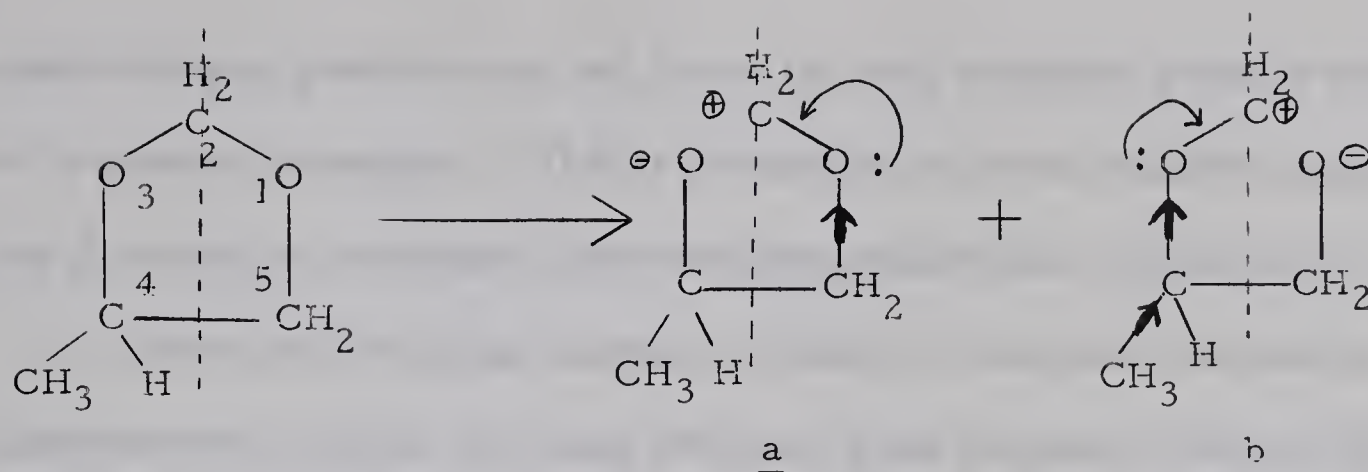


Chart 30

inductive effect of the equivalent of a methyl group, (heavy type), while ion b is stabilized by the inductive effect of a unit which approximates the ethyl group (heavy type). Since an ethyl group is a better electron donor than is a methyl group, ion b is more stable than ion a, hence hydrogenolysis by ring cleavage via b should predominate. This is the observed result (93%) (1). Some of the product arising via ion a also is formed (7%).

If one writes the structure of the 2-alkoxytetrahydrofuran in the same way (Chart 31), using the same approach (44) one sees that the

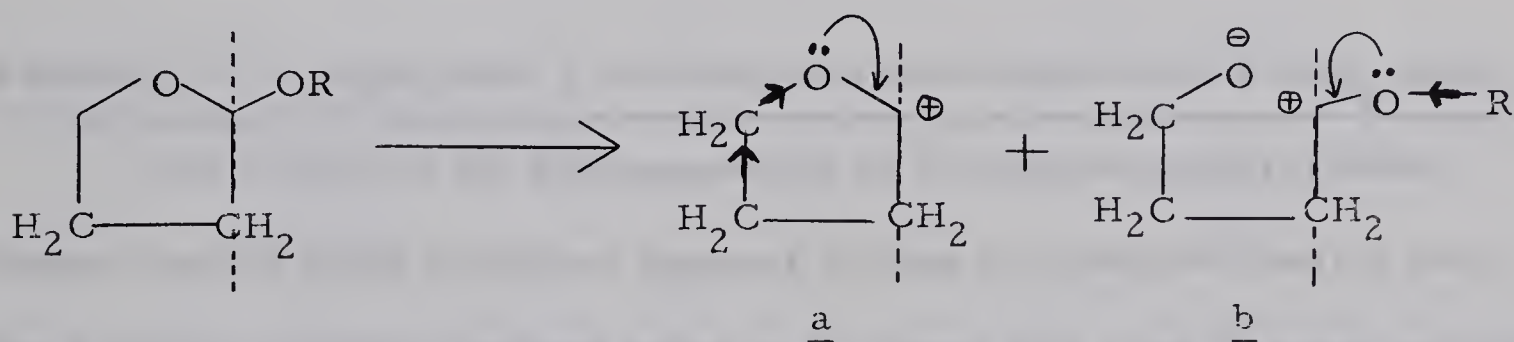


Chart 31

ion a obtained by exo C-O bond cleavage is stabilized by the equivalent of an ethyl group (heavy type) while the ion formed by ring cleavage (ion b) is stabilized by the group R. If now R is methyl, one would

expect ion a to predominate and hence the ring retention product would be in greater abundance. If R is t-butyl the reverse would be expected. For R = ethyl or isopropyl, intermediate proportions should occur.

Since only the ring cleavage product is found and this nearly quantitatively, neither the polar effects (1) nor the steric effects (2) appear to control the direction of the reaction. The fact that tetrahydrofuran is a better electron donor (a stronger base) than dimethyl ether, diethyl ether or diisopropyl ether, may be responsible for the results observed. That the basic strength of these ethers decreases in this order has been shown (51) during studies of the relative stability of their boron fluoride complexes. (The dissociation constants $\times 100$ of these complexes are 0.0011, 0.184, 0.420 for tetrahydrofuran, dimethyl ether and diethyl ether (51)). The Lewis acid will therefore associate with the ring oxygen nearly exclusively and give as a result only ring opening reduction products.

Reduction of 5-substituted-2-methoxytetrahydrofurans with LiAlH_4 - AlCl_3 .

The results of the hydrogenolysis of 2-alkoxytetrahydrofurans shows that the polar character appears to have no dominant control over the direction of bond cleavage since in all cases only ring cleavage products are obtained. Since an electron-donating and an electron-withdrawing substituent at position 5 might influence the direction of reaction, 2-methoxy-5-methyltetrahydrofuran and 2-methoxy-5-methoxymethyltetrahydrofuran were hydrogenolysed. The results of these experiments are

given in Table IV.

Experiment 1 in Table IV shows that the presence of the methyl group at position 5, has resulted in a preponderance of exo C-O bond cleavage in the proportion exo/endo = 60/40. This is in sharp contrast to the apparently exclusive ring cleavage occurring when the C₅ position is unsubstituted (Expt. 1, Table III). The increase in the amount of exo C-O bond cleavage resulting in ring retention, is in agreement with the polar influence of the C₅ methyl group which in this case outweighs to some extent the influence which caused nearly exclusive ring cleavage in the 2-alkoxytetrahydrofurans (Table III). If one writes the two possible routes of reaction as in Chart 32, it is clearly apparent that the transition

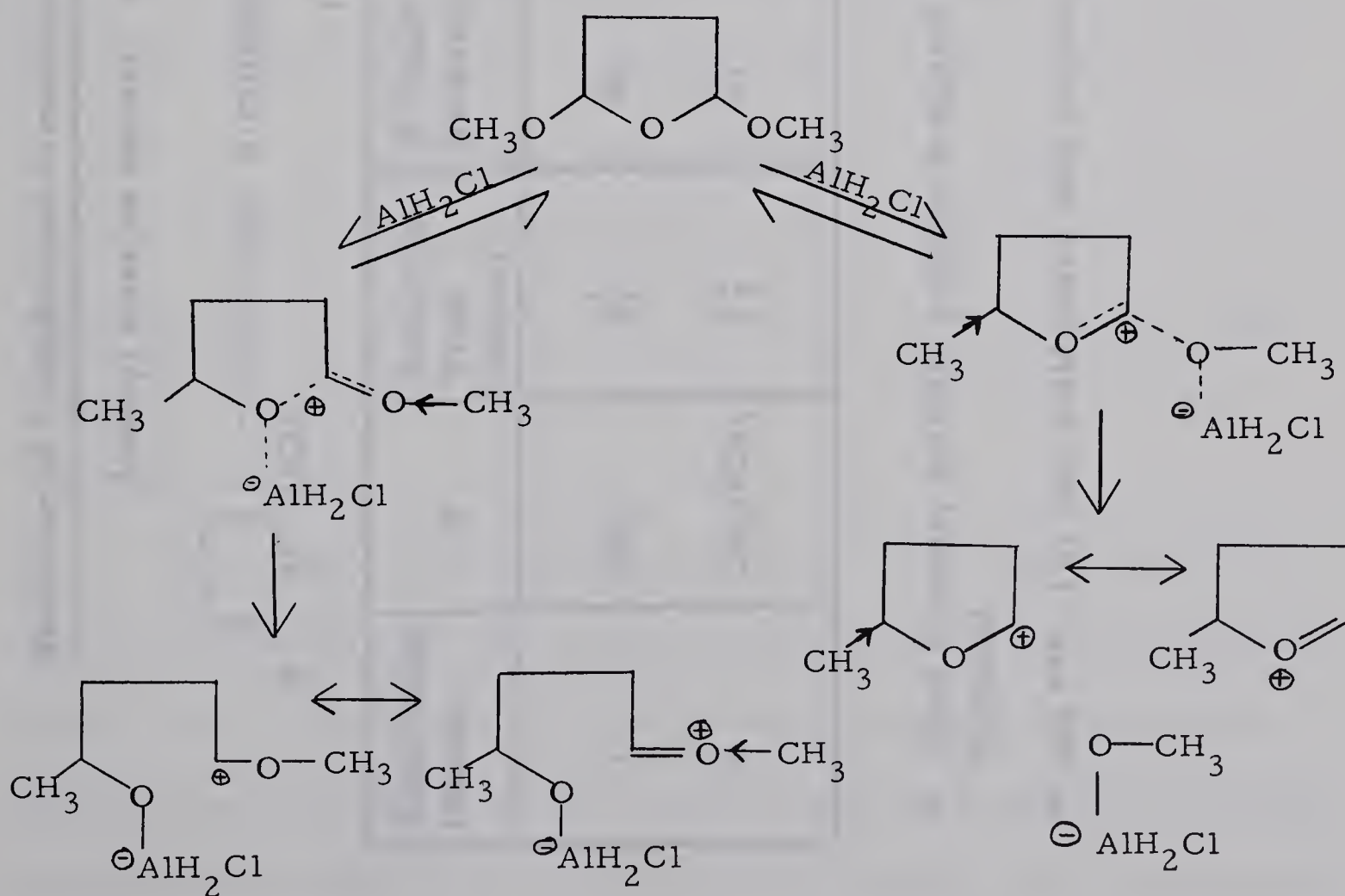
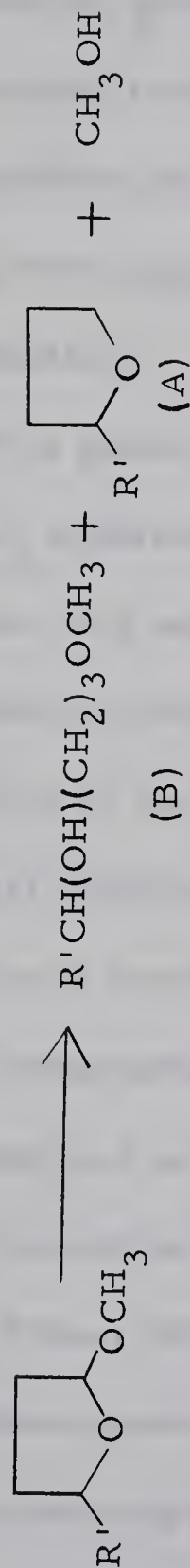


Chart 32

TABLE IV

Reduction of 5-substituted-2-methoxytetrahydrofurans with $\text{LiAlH}_4\text{-AlCl}_3$.

(diethyl ether as solvent; at room temperature)



Experiment Number	R'	Reduction Time (hours)	% Total* Recovery	% Recovered Starting Material	% Yield** of B	% Yield*** of A
1	CH ₃	$2\frac{1}{4}$	80	0	40	60
2	CH ₂ OCH ₃	$2\frac{1}{4}$	93	0	100	0

* Total recovery includes both the reduction products and the recovered starting material.

** and *** Per cent yield based upon recovered reduction products.

state involving exo C-O bond cleavage is more readily attained due to the additional stabilization offered by the electron-donating effect of the C₅ methyl group. The ease of attainment of the alternate transition state, arising from endo C-O bond cleavage is not enhanced by the electron donor properties of the C₅ methyl group. On this basis, the former route should be favoured and this is precisely what is found experimentally.

It is possible that steric effects due to the presence of both the C₂ and C₅ substituents would affect the ease of approach of the Lewis acid to the ring oxygen and hence influence the ease of attainment of the transition state and hence the intermediate oxocarbenium ion. The introduction of the CH₃-OCH₂- group at C₅, should offer at least as much steric interference as is caused by the C₅ methyl group and this should hinder approach of the Lewis acid to the ring oxygen, giving rise again to preferential exo bond cleavage. This group, however is electron withdrawing and on this latter basis the transition state leading to ring retention should be less easily attained than is that leading to ring cleavage (Chart 33).

Experiment 2 (Table IV) shows that the only product obtained was that from ring cleavage. Ring retention products were not detected even in trace amounts, by gas liquid chromatography. This seems to indicate that the group at C₅ does not offer significant steric interference to the approach of the Lewis acid to the ring oxygen. Hence polar effects of the C₅ group in 2-alkoxytetrahydrofurans appears to exert a pronounced

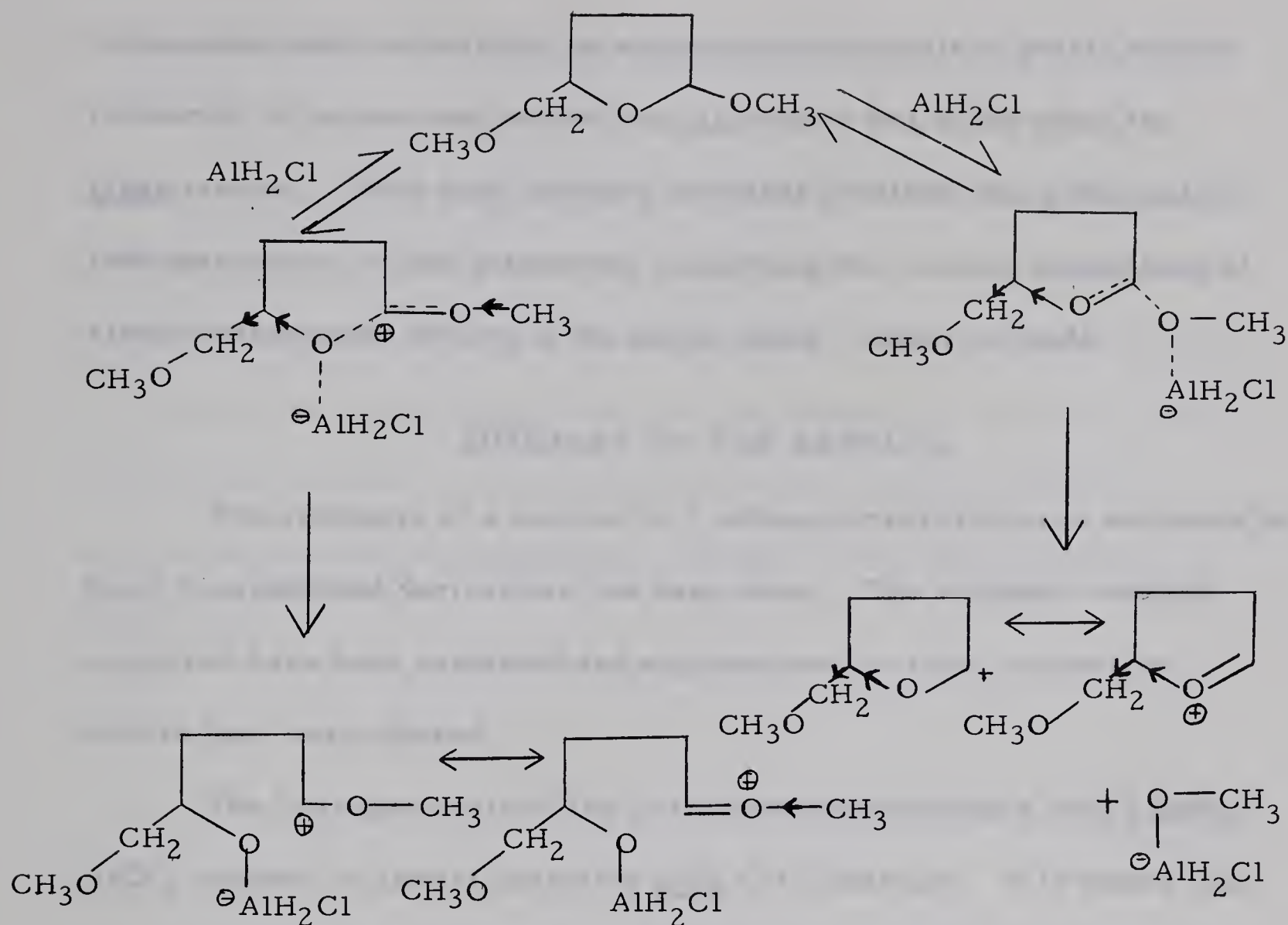


Chart 33

effect in the direction of C-O bond cleavage during hydrogenolysis by $\text{LiAlH}_4\text{-AlCl}_3$.

The flaw in the above arguments is that both the cis and trans isomers of the two C_5 substituted 2-methoxytetrahydrofurans have not been isolated and individually subjected to the hydrogenolysis reaction. We do not know whether we are dealing with a mixture of cis and trans isomers in each of the two cases or with cis in one and trans in the other or with the cis (or trans) isomers in both cases. Attempts to separate these by gas liquid chromatography were unsuccessful.

The hydrogenolysis results obtained from the two C_5 substituted

compounds could conceivably be explained on the basis of steric effects primarily, if in one case we had the cis isomer and in the other the trans isomer. Until both isomers are made available and subjected to hydrogenolysis, a final discussion concerning the relative importance of steric versus polar effects in the above cases, cannot be made.

SUMMARY OF THE RESULTS.

The synthesis of a number of 2-alkoxytetrahydrofurans and some of their 5-substituted derivatives has been done. The synthetic methods employed have been examined and explanations for their success or failure have been offered.

The hydrogenolysis of the 2-alkoxytetrahydrofurans with LiAlH_4 - AlCl_3 resulted in almost exclusive endo C-O cleavage. It is known that tetrahydrofuran is a stronger base than dimethyl ether, diethyl ether and diisopropyl ether. The Lewis acid therefore coordinates almost exclusively with the ring oxygen to give only ring cleavage products. Steric and electronic effects of the alkyl groups attached to the exo oxygen do not appear to play a dominant role.

However, the hydrogenolysis of 2-methoxy-5-methyltetrahydrofuran gave more exo cleavage (60/40 = exo/endo). This is explained in terms of the probable greater ease of attainment of the transition state involving exo C-O bond cleavage due to the additional stabilization offered by the electron-donating effect of the C_5 methyl group. The ease of attainment of the alternate transition state, arising from endo C-O bond cleavage is

not enhanced by the electron donor properties of the C₅ methyl group.

The methoxymethyl group (an electron withdrawing group) at position 5 resulted in ring cleavage exclusively. This seems to indicate that the group at C₅ does not offer significant steric interference to the approach of the Lewis acid to the ring oxygen. However since attempts to separate the cis and trans isomers of both the 5-substituted compounds were not successful, it is not possible to make a definite decision concerning the relative importance of steric versus polar effects in these cases.

EXPERIMENTAL

All boiling points and melting points in this work are uncorrected.

All gas liquid chromatographic analyses were made with an F and M model 700 laboratory chromatograph on a 6 ft by 1/16 in (inside diameter) column, filled with 20% Carbowax 20M on Gas Chrom P (60-80 mesh) at a helium gas flow rate of 50 ml/min. The column temperature was dependent upon the boiling point of the compound analysed. The compounds were identified by comparison of their gas liquid chromatography retention times as well as their infrared and n.m.r. spectra with those of authentic samples. Quantitative analyses were made by comparison of peak areas with those obtained from known and weighed artificial mixtures.

Infrared spectra were recorded with a Perkin-Elmer model 421 instrument.

Nuclear magnetic resonance (n.m.r.) spectra were recorded with Varian Associates A-60 and HR-100 Spectrometers operated by Mr. R. Swindlehurst and assistants.

Elemental analysis was done by Mrs. Darlene Mahlow.

PART I. PREPARATION OF THE ACETALS.

A. The 2-Alkoxytetrahydrofurans.

3-Carbomethoxy-2-methoxytetrahydrofuran was prepared by the method described in the literature by Korte and Machleidt (10).

Sodium metal (35 g, 1.6 g. atom) was heated to its melting point in xylene and then stirred at high speed during the cooling process to promote the formation of small particles of metal. The powdered sodium was washed several times with anhydrous ether and finally suspended in 300 ml of diethyl ether containing 3 ml of absolute ethanol. The mixture was then stirred for 2 hours. A solution of γ -butyrolactone (130 g, 1.6 mole) and ethyl formate (120 g, 1.6 mole) in 600 ml of diethyl ether was then added dropwise to the stirred suspension of sodium at room temperature. The resulting pale yellow mixture, when left standing overnight, deposited a yellow solid. When removed by filtration the sodium salt weighed 206 g. The salt was used without further purification.

The crude sodium salt was added to 1250 ml of methanol containing 91 g of dry hydrogen chloride. The hydrogen chloride had been bubbled into the cold methanol until the desired increase in weight was obtained. The mixture was stirred at room temperature for about 8 hours and then refluxed for an additional 12 hours. It was then allowed to stand at room temperature for 24 hours. Excess methanol

was removed via a rotatory evaporator. The precipitated sodium chloride was removed by filtration and washed with ether. The combined filtrate and ether wash was poured into a cold aqueous solution of potassium carbonate (5%) and stirred until all the acid was destroyed. The alkaline solution was extracted three times with ether and the combined ether extracts washed twice with a concentrated solution of sodium chloride, and then once with water. The ether layer was then dried over anhydrous magnesium sulfate. The ether solution was filtered from the sulfate and the ether removed by use of a rotatory evaporator. The residue was distilled under reduced pressure giving 145 g (90%) of material boiling at 94° at 15 mm; η_D^{25} , 1.4357. Lit. b.p., 81° at 13 mm (10).

3-Carboxy-2-methoxytetrahydrofuran was prepared according to the procedure described in the literature by Korte and Machleidt (10).

The ester, 3-carbomethoxy-2-methoxytetrahydrofuran (217 g) was stirred overnight at room temperature with 99 g of potassium hydroxide in 500 ml of water. The mixture was then acidified with 6N aqueous sulfuric acid and saturated with ammonium sulfate. The oil which separated was carefully decanted and the aqueous layer extracted three times with ether. The combined ether extracts and the oil was washed twice with a saturated solution of sodium chloride. The ether layer was dried over anhydrous magnesium sulfate, filtered from the

sulfate and the ether removed using a rotatory evaporator. The residue, the crude acid, was an oil weighing 131 g (approximately 66% yield).

2-Methoxytetrahydrofuran was prepared following an observation by Korte and Machleidt (10) that 3-carboxy-2-methoxytetrahydrofuran decarboxylates at room temperature to give 2-methoxytetrahydrofuran and 2,3-dihydrofuran. The same observation was made by us in an attempted distillation of the acid during the course of this work.

The crude 3-carboxy-2-methoxytetrahydrofuran (128 g) was heated at 100-120° in a flask equipped with a condenser for downward distillation. Carbon dioxide was evolved during the heating. A fraction, which was mainly 2-methoxytetrahydrofuran, was collected in an ice-cooled receiver connected to the condenser by a ground glass adapter. A dry ice-acetone trap attached to the exit of the first receiver collected about 5 g of 2,3-dihydrofuran. The 2-methoxytetrahydrofuran was fractionally distilled with a spinning band column and provided 34 g (38%) of pure material. B.p., 101-102° at 699 mm; η_D^{24} , 1.4104. Lit.b.p., 105-107°; η_D^{14} , 1.4132 (45).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.82; H, 9.89.

Found: C, 58.96; H, 9.82.

3-Carbethoxy-2-ethoxytetrahydrofuran was prepared according to the method just described (10) in detail for the synthesis of the methyl ester with slight modifications. The molar proportions of the starting

materials were the same but a greater excess of ethanol was used.

The ester obtained (41%) was an oil, b.p. , 110° at 19 mm; n_D^{25} , 1.4318.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.49; H, 8.51.

Found: C, 57.19; H, 8.43.

2-Ethoxytetrahydrofuran was prepared by the decarboxylation of 3-carboxy-2-ethoxytetrahydrofuran as described above for 2-methoxytetrahydrofuran. An oil was obtained (29%), b.p. , $110-112^{\circ}$ at 699 mm; n_D^{26} , 1.4105. Lit. b.p. 125° ; n_D^{20} , 1.4149 (53).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.06; H, 10.34.

Found: C, 62.12; H, 10.80.

3-Carboisopropoxy-2-isopropoxytetrahydrofuran was prepared as described above (10) for the ethyl ester. The crude ester lost isopropyl alcohol on distillation since it did not show an absorption at 1650 cm^{-1} before distillation but showed this absorption after distillation in its infrared spectrum. An oil was obtained (29% yield), b.p. , $108-110^{\circ}$ at 15 mm. The refractive index was not determined since the ester was not pure.

2-Isopropoxytetrahydrofuran was prepared by the decarboxylation of 3-carboxy-2-isopropoxytetrahydrofuran. An oil was obtained (30%), b.p. , $117-119^{\circ}$ at 699 mm; n_D^{24} , 1.4109. Lit. b.p. 132° ; n_D^{20} ,

1.4147 (53).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.50; H, 10.76.

Found: C, 64.30; H, 10.73.

Attempted preparation of 2-t-butoxy-3-carbo-t-butoxytetrahydrofuran.

The preparation of this compound by the method used to prepare the methyl, ethyl and isopropyl homologues failed. Treatment of the sodium salt of the formylated γ -butyrolactone with t-butyl alcohol and hydrogen chloride gave the desired ester as shown by the infrared spectrum of the crude product. Distillation of the crude ester resulted in the elimination of t-butyl alcohol to give a crystalline solid shown by its spectra and elemental analysis to be 3-carbo-t-butoxy-4,5-dihydrofuran. The infrared absorption at 1660 cm^{-1} and the n.m.r. signal at τ 2.5 indicated the vinyl ether structure. M.p. , $45-46^\circ$.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.55; H, 8.23.

Found: C, 63.49; H, 8.15

2-t-Butoxytetrahydrofuran was prepared by a modification of the procedure described in the literature by Eliel and coworkers (2).

A quantity of 2,3-dihydrofuran (obtained as shown in Chart 16, see also below) (8 g, 0.11 mole) was cooled and added to anhydrous t-butyl alcohol (dried over sodium) (16.3 g, 0.22 mole) in the presence of a trace of hydrochloric acid. The mixture was stirred at room

temperature for 6 hours. A small amount of solid sodium bicarbonate was added to neutralize the acid. The mixture was then fractionated, using a spinning band column, giving 10 g (62%) of pure 2-t-butoxy-tetrahydrofuran. B.p. , 126-127° at 699 mm; η_D^{25} , 1.4171. Lit. b.p. , 36-40° at 10 mm; η_D^{20} , 1.4186 (2).

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.61; H, 11.70.

Found: C, 66.82; H, 11.60.

B. Preparation of some dihydrofurans as byproducts.

3-Carbomethoxy-4,5-dihydrofuran was prepared by modifying the procedure described in the literature by Korte and Machleidt (10).

3-Carbomethoxy-2-methoxytetrahydrofuran (144 g), containing 1 drop of concentrated sulfuric acid, was heated at 125° in a flask fitted with a condenser arranged for downward distillation. The temperature was maintained until the methanol ceased to distil. The residue was first neutralized with a small amount of solid sodium bicarbonate, then crystallized from Skellysolve B. Yield, 92 g (80%). M.p. , 34-35°. Lit. m.p. , 36-37° (10).

3-Carboxy-4,5-dihydrofuran was prepared by modifying the procedure described by Korte and Machleidt (10).

3-Carbomethoxy-4,5-dihydrofuran (92 g) was stirred overnight, at room temperature, with 50 g of potassium hydroxide in 300 ml of

water. The mixture was then poured with stirring into 8N hydrochloric acid. A white precipitate appeared. This was separated by filtration under suction and washed with water, and then crystallized from methanol. Yield, 56 g (68%). M.p., 176° . Lit. m.p., 176° (10).

2,3-Dihydrofuran was prepared by merely heating the acid, 3-carboxy-4,5-dihydrofuran, following an observation (10) that the acid decarboxylated at room temperature.

3-Carboxy-4,5-dihydrofuran (20 g) was heated to about 200° .

The highly volatile product was collected in a dry ice-acetone trap, giving 8 g (66%) of pure 2,3-dihydrofuran. B.p., $52-53^{\circ}$ at 699 mm; η_D^{23} , 1.4204. Lit. b.p., $53-55^{\circ}$ at 745 mm; η_D^{20} , 1.4200 (2).

C. The 5-substituted 2-methoxytetrahydrofurans.

3-Carbomethoxy-5-methyl-2-methoxytetrahydrofuran was prepared by the method described by Korte et al (11); which was similar to the method used by Korte and Machleidt (10) for the preparation of 3-carbomethoxy-2-methoxytetrahydrofuran. Yield, 55%; b.p., 97° at 20 mm; η_D^{26} , 1.4310. Lit. b.p., 84° at 9 mm (11).

3-Carboxy-5-methyl-2-methoxytetrahydrofuran. The method described for the preparation of 3-carboxy-2-methoxytetrahydrofuran, following the published procedure (10), was used to obtain this acid from the above ester. The acid, an oil, obtained in 92% yield, decarboxylated on

attempted purification by distillation. It was subjected to the next step in the crude form.

5-Methyl-2-methoxytetrahydrofuran. The method described for the preparation of 2-methoxytetrahydrofuran was employed to make this acetal by the decarboxylation of 3-carboxy-5-methyl-2-methoxytetrahydrofuran. Yield, 42%. B.p., 108-109° at 699 mm; n_D^{30} , 1.4127. Anal. Calcd. for $C_6H_{12}O_2$: C, 62.06; H, 10.34. Found: C, 62.11; H, 10.54.

2-Methoxy-5-methoxymethyltetrahydrofuran.

Method I (unsuccessful).

2,5-Dihydro-2,5-dimethoxyfurfuryl alcohol was prepared following the procedure described in the literature by Clauson-Kaas and Limborg (12).

Furfuryl alcohol (98 g, 1 mole) and potassium acetate (200 g, 2 moles) were dissolved in 600 ml of anhydrous methanol contained in a three neck round bottom flask fitted with a reflux condenser and a drying tube. The mixture was cooled to -7°. A solution of bromine (50 ml, 1.82 moles) in 500 ml of anhydrous methanol was added dropwise with stirring. After the addition was completed (about 1 hour) the resulting mixture was stirred for about 15 minutes and then poured into ice-cold, saturated aqueous calcium chloride. The mixture was

extracted with ether, the ether extract neutralized with a solution of potassium carbonate and then dried over a mixture of anhydrous sodium sulfate and anhydrous potassium carbonate. The solid was separated by filtration and the ether was removed from the filtrate via a rotatory evaporator. Distillation of the residue under vacuum gave 40 g (25%) of material boiling at $87-88^{\circ}$ at 0.4 mm; η_D^{30} , 1.4569. Lit. b.p., $86-87^{\circ}/0.4$ mm; η_D^{25} , 1.4600 (12)

2,5-Dihydro-2,5-dimethoxyfurfuryl methyl ether. The preparation of this material follows the general method described by Brown et al (36) for the methylation of hydroxyl groups.

2,5-Dihydro-2,5-dimethoxyfurfuryl alcohol (20 g, 0.125 mole) and methyl iodide (31 g, 0.22 mole) were dissolved in 200 ml of 1,2-dimethoxyethane contained in a three neck flask equipped with a reflux condenser and a drying tube. The solution was cooled to $<15^{\circ}$ and sodium hydride (4.8 g, 0.20 mole) was added in portions at such a rate that the temperature of the reaction mixture did not exceed 15° . After the addition of the sodium hydride, the mixture was stirred for about two hours during which time it was allowed to come to room temperature. Excess sodium hydride was destroyed by slowly adding methanol to the cooled reaction mixture. Excess 1,2-dimethoxyethane was removed via a rotatory evaporator. Anhydrous ether was added to the residue and the precipitated sodium iodide was separated by filtration. The ether

was removed from the filtrate and the residue distilled under vacuum. Yield, 18 g (80%). B.p. , 86° at 10 mm; η_D^{25} , 1.4367. Lit. b.p. , 84° at 10 mm; η_D^{25} , 1.4383 (17).

Method Ia.

Methyl 5-methoxyfurfuryl ether. An attempted synthesis of this material was done following in detail the procedure described in the literature (19).

2,5-Dihydro-2,5-dimethoxyfurfuryl methyl ether (10 g, 0.56 mole) was mixed with 0.25 g of ortho-phosphoric acid. The mixture was added dropwise to a mixture of n-butyl phthalate and 0.25 g of ortho-phosphoric acid previously heated to 250° . The addition of each drop caused a considerable amount of charring. A distillate was collected. Analysis by gas liquid chromatography showed 6 peaks one of which was the major peak. The major peak was collected and its n.m.r. spectrum is shown in Fig. 1 (page 22). As the spectrum shows, the major peak was not the expected product.

Method Ib.

Methyl 5-methoxyfurfuryl ether. An attempt to obtain this material was made by modifying the pyrolysis procedure described above.

2,5-Dihydro-2,5-dimethoxyfurfuryl methyl ether (9.8 g) containing about 0.10 g of p-toluenesulfonic acid was stirred for 48 hours while

the temperature of the reaction mixture was maintained between 70-100°. Methanol distilled over. Analysis by gas liquid chromatography of the residue indicated the presence of the starting material plus a new peak. The residue was fractionally distilled using a spinning band column to give a 40% yield of a new product boiling at 86° at 40 mm; η_D^{29} , 1.4575. This product was shown by n.m.r. and by comparison with an authentic sample to be furfuraldehyde dimethyl acetal, b.p., 57-58° at 14mm; η_D^{25} , 1.4486 (17).

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.15; H, 7.04.

Found: C, 59.08; H, 6.83.

Method II (unsuccessful).

Methyl 2-furoate was prepared according to published directions (38) as follows.

2-Furoic acid (112 g, 1 mole) in methanol (1.5 moles, 60 ml) containing 1 ml of concentrated sulfuric acid, was stirred under reflux until the furoic acid was dissolved. About 100 ml of toluene was added, as well as 19 ml of concentrated sulfuric acid and the mixture was refluxed overnight. Two layers were formed. The lower layer was separated and extracted twice with toluene. The toluene extracts were combined with the upper layer (toluene) and dried over anhydrous sodium sulfate. After the drying agent was separated, the toluene was removed and the residue distilled under vacuum. Yield, 92 g (69%). B.p., 83°

at 28 mm; n_D^{25} , 1.4853. Lit. b.p., 181° , n_D^{20} , 1.4860 (52).

Methyl 5-bromo-2-furoate. Bromination of methyl 2-furoate was carried out according to the published procedure described by Amstutz and Petfield (20).

Methyl 2-furoate (176 g, 1.4 moles) in a three neck flask equipped with stirrer and a reflux condenser was heated on a steam bath. Bromine (63 ml, 2.36 moles) was added dropwise over a period of 1 hour to the rapidly stirred solution. Towards the end of the bromine addition a solid separated. When all the bromine had been added the mixture was stirred for another 10 minutes and then cooled. The resulting solid was collected and washed with cold water and then steam distilled. The colourless solid which was obtained from the distillate was crystallized from a mixture of dioxane and water. M.p., $62-63^\circ$. Lit. m.p., 63° (20). Yield, 125 g (44%). The solid residue which remained in the steam distillation flask was essentially 5-bromo-2-furoic acid (20). This was crystallized from water to give 45 g of pure 5-bromo-2-furoic acid and melting at $185-186^\circ$. Lit. m.p., $186-187^\circ$ (20).

Methyl 5-methoxy-2-furoate was prepared according to the published procedure described by Amstutz and Manly (21).

Methyl 5-bromo-2-furoate (12.3 g, 0.06 mole) was added to a solution of sodium methoxide previously prepared by dissolving 1.61 g of sodium metal in 100 ml of anhydrous methanol. The mixture was

heated in an autoclave at 100° for $1\frac{1}{2}$ hours. After the mixture had cooled to room temperature (about 40 minutes), the mixture was removed and most of the methanol removed via a rotatory evaporator. The residue was poured into water. The ether extract of this mixture was dried over anhydrous sodium sulfate and the drying agent removed by filtration. The ether was removed in a rotatory evaporator. Gas liquid chromatography of the residue indicated that it was a mixture of only 2 compounds, the methoxy ester and the unchanged bromo ester in the ratio 3/2. Attempts to separate the substances by distillation of the 3/2 mixture were not successful since the compounds are solids at room temperature. Although the distillation apparatus was heated with steam, the compounds solidified on the adapter rendering their distillation extremely difficult. Yield of the methoxy ester was 40%. Enough pure material was obtained by gas liquid chromatography to characterize the ester. M.p., $50-51^{\circ}$. Lit. m.p., $51-53^{\circ}$ (21).

Methyl 5-methoxyfurfuryl alcohol was prepared according to the published procedure described by Amstutz and Manyl (21).

The mixture of 5-bromo-2-furoate and 5-methoxy-2-furoate (20 g) containing 60% (12 g) of the latter ester, was dissolved in 50 ml of anhydrous ether. The solution was added dropwise to a rapidly stirred suspension of LiAlH_4 (3.64 g) in anhydrous ether. After the addition of the ester solution, the resulting mixture was refluxed for

$1\frac{1}{2}$ hours. To the cooled solution was added slowly 8 ml of a 15% aqueous solution of sodium hydroxide. The ether layer was decanted and the precipitate was heated in refluxing ether for about 2 hours. The combined ether extracts were dried over anhydrous sodium sulfate. The ether was removed in a rotatory evaporator and the residue was fractionally distilled under vacuum giving 6.9 g (75%) of 5-methoxyfurfuryl alcohol boiling at $110-112^{\circ}$ at 13 mm; η_D^{26} , 1.4882. Lit. b.p., $112-115^{\circ}$ at 15 mm (21).

Methyl 5-methoxyfurfuryl ether. The methylation of 5-methoxyfurfuryl alcohol was accomplished by the procedure employed for the methylation of 2,5-dihydro-2,5-dimethoxyfurfuryl alcohol already described (36).

Yield, 63%. B.p., $90-92^{\circ}$ at 40 mm; η_D^{26} , 1.4623. Lit. b.p., $93-100^{\circ}$ at 60 mm; η_D^{21} , 1.4620 (19).

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09.

Found: C, 59.10; H, 6.99.

Hydrogenation of methyl 5-methoxyfurfuryl ether. The attempted hydrogenation of this compound was performed using rhodium on alumina as catalyst, according to a published procedure employed by Stocker (26) for the hydrogenation of aromatic ethers and alcohols containing C-O linkages susceptible to hydrogenolysis.

A mixture of methyl 5-methoxyfurfuryl ether (6 g, 0.035 mole) and rhodium on alumina catalyst (1.5 g) in 40 ml of methanol in a Parr

hydrogenation apparatus was shaken at room temperature with hydrogen at 50 p.s.i. . . . After 15 minutes the required amount of hydrogen had been absorbed. The mixture was removed from the hydrogenation apparatus, filtered and the methanol removed from the filtrate by fractionation with a spinning band apparatus. The residue was distilled under reduced pressure and gave 5.2 g (86%) of a compound boiling at 70° at 13 mm; η_D^{23} , 1.4160. This material was shown by comparison of its physical constants with literature values to be methyl 5-methoxyvalerate. Lit. b.p., $70-71^{\circ}$ at 11 mm; η_D^{20} , 1.4150 (47).

2-Methoxy-5-methoxymethyltetrahydrofuran.

Method III. (successful).

2,3-Dihydro-6-methoxymethylpyran was prepared by the methylation of 2,3-dihydro-2-hydroxymethyltetrahydropyran, using the procedure already described (36). Yield 75%. B.p., $58-60^{\circ}$ at 20 mm; η_D^{23} , 1.4545. Lit. b.p., 60° at 20 mm; $\eta_D^{17.5}$, 1.4508 (46).

2,3-Dihydroxy-6-methoxymethylpyran was prepared using a procedure published in the literature (41).

To a solution of m-chloroperoxybenzoic acid (67.66 g, 0.39 mole) in 500 ml of water-saturated ether at 0° , was added 2,3-dihydro-6-methoxymethylpyran (57 g, 0.5 mole) dropwise. After 24 hours the mixture was extracted with water and the aqueous layer extracted with

ether to remove m-chlorobenzoic acid. The water was removed using the rotatory evaporator at 40° and 12 mm, to yield about 51 g of crude diol. The diol was not distilled since it was possible that it might lose water, but was subjected to the next step in the crude form.

2-Hydroxy-5-methoxymethyltetrahydrofuran.

To a solution of periodic acid (24.96 g, 0.13 mole) in 300 ml of a 1:1 mixture of water and dioxane, was added the crude 2,3-dihydroxy-6-methoxymethyltetrahydrofuran (21 g, 0.13 mole). The mixture was stirred at room temperature for about 12 hours. Solid sodium bicarbonate was then added to neutralize excess periodic acid and formic acid formed from the reaction, until the mixture was slightly alkaline. The mixture was then extracted continuously with chloroform for about 24 hours. The chloroform layer was separated, dried over sodium sulfate and sodium thiosulfate (to remove any liberated iodine). The chloroform was removed by fractional distillation and about 13 g of residue remained. The infrared spectrum of the residue showed both hydroxyl and carbonyl peaks at 3450 cm^{-1} and 1730 cm^{-1} respectively. Attempts to distill the crude product resulted in the appearance of unsaturation as shown by the infrared spectrum of the distillate. The crude product was therefore subjected to the next step undistilled.

2-Methoxy-5-methoxymethyltetrahydrofuran.

Crude 2-hydroxy-5-methoxymethyltetrahydrofuran (about 12 g)

was stirred at room temperature for about 6 hours with an excess of anhydrous methanol in the presence of a few drops of concentrated hydrochloric acid. Solid sodium bicarbonate was then added to neutralize the acid. The methanol was removed by fractional distillation and the residue distilled under reduced pressure to give 8.5 g (73% yield based on the crude 2-hydroxy-5-methoxymethyltetrahydrofuran) of a colorless liquid. B.p., 90-93° at 140 mm; η_D^{23} , 1.4248.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.59; H, 9.65.

Found: C, 57.55; H, 9.59.

5-Isopropyl-2-methoxytetrahydrofuran.

Method I (unsuccessful).

α,α -Dimethyl-5-methoxyfurfuryl alcohol. The attempted synthesis of this compound was done according to a procedure described by Reichstein et al (22) for the synthesis of α,α -dimethylfurfuryl alcohol.

Methyl 5-methoxy-2-furoate (20 g, 0.13 mole) dissolved in 50 ml of anhydrous ether was added dropwise to a cold (0°) solution of methyl magnesium iodide (prepared from 60 g of methyl iodide and 9.3 g of magnesium metal). The mixture was then allowed to stand overnight and then decomposed with ice water. After addition of excess potassium carbonate to the solution, the mixture was steam distilled. The product was salted out from the distillate with potassium carbonate and extracted with ether. The ether extract was dried over anhydrous sodium sulfate

and anhydrous potassium carbonate. The ether was removed via the rotatory evaporator and the residue distilled under reduced pressure to give 3 fractions. The n.m.r. spectrum of each fraction did not show the vinyl protons characteristic of the furan ring.

Method II (unsuccessful).

γ,γ -Dimethylacetoacetic ester was prepared according to a published procedure described by Korte and coworkers (42).

Ethyl acetoacetate (260 g, 2 moles) was added to sodium methoxide (46 g of sodium metal in 800 ml of absolute ethanol). The ethanol was distilled off and the remaining cake was suspended in anhydrous ether. Isobutyryl chloride (212 g, 2 moles) was added dropwise to the suspension at such a rate that the ether solution refluxed gently. The precipitated sodium chloride was filtered off. The filtrate was diluted with water and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and the ether was removed via the rotatory evaporator. The residue was distilled under reduced pressure to give a colorless oil (184 g, 46%). B.p., 112-114° at 16 mm; n_D^{25} , 1.4515. Lit. b.p., 114° at 16 mm (42).

To sodium methoxide (20 g of sodium metal in 60 ml of absolute ethanol) was added dropwise with stirring isobutyrylacetoacetic ester (180 g) prepared as described above. The mixture was allowed to stand at room temperature for 3 days. Excess ethanol was removed in

the rotatory evaporator. The residue was neutralized with dilute hydrochloric acid, extracted several times with ether and the combined ether extracts were dried over anhydrous sodium sulfate. The ether solution was filtered from the sodium sulfate and the ether removed. The residue was distilled under reduced pressure to give γ,γ -dimethylacetoacetic ester (85 g, 60%) boiling at 82-84° at 14 mm; n_D^{25} , 1.4235. Lit. b.p., 83-86° at 13 mm (42).

Diethyl α -isobutyrylsuccinate was prepared by modifying a procedure described by Korte and coworkers (42).

To a solution of sodium metal (9.66 g, 0.42 g. atom) in 300 ml of absolute ethanol at 10°, was added slowly γ,γ -dimethylacetoacetic ester (82.16 g, 0.52 mole). The mixture was stirred for about 1 hour, then ethyl chloroacetate (51.66 g, 0.42 mole) was added while the mixture was cooled in ice. The mixture was then refluxed until it was neutral to litmus (6 hours). The precipitated sodium chloride was filtered off and washed with ethanol. The filtrate and the washings were combined and the ethanol was removed by distillation. Attempted distillation of the ester on a small scale resulted in decarboxylation. The ester was therefore not isolated but was subjected to the next step in the crude form.

Ethyl β -isobutyrylpropionate was prepared by modifying a procedure described in the literature by Korte and coworkers for analogous

compounds (42).

The crude diethyl α -isobutyrylsuccinate from the experiment described above was refluxed with 30 ml of concentrated sulfuric acid in 200 ml of water for 12 hours. When cooled the aqueous layer was saturated with ammonium sulfate and the oil that separated was extracted three times with ether. The combined ether extracts were dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the ether removed from the filtrate in the rotatory evaporator. The remaining oil, the acid, was then heated with 300 ml of absolute ethanol and 30 ml of concentrated sulfuric acid for 12 hours. Excess ethanol was distilled off and the residue was neutralized with an aqueous solution of sodium bicarbonate. The aqueous layer was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the ether removed from the filtrate by evaporation in the rotatory evaporator. The residue was distilled under reduced pressure to give 40 g of the ketoester boiling at 113-114^o at 21 mm; η_D^{25} , 1.4250. Lit. b.p., 113-114^o at 21 mm (42).

Ethyl γ -hydroxy- γ -isopropylbutyrate.

The above keto ester (37.43 g, 0.22 mole) was placed in 300 ml of methanol cooled to 0^o. Sodium borohydride (4.17 g, 0.11 mole) was added in small portions while the mixture was stirred vigorously. Hydrogen was evolved. After the addition of sodium borohydride was

completed, the mixture was stirred at 0° for 4 hours and then acidified to pH 4-6 with dilute hydrochloric acid. Excess methanol was removed in the rotatory evaporator. The infrared spectrum of the crude hydroxyester showed two carbonyl bands at 1770 cm^{-1} and 1730 cm^{-1} which correspond to the lactone and the hydroxyester respectively.

The hydroxyester was not isolated but was treated with a drop of polyphosphoric acid and then distilled under reduced pressure. Ethanol was eliminated to give material boiling at 98° at 15 mm; η_{D}^{25} , 1.4337. This should be γ -isopropyl- γ -butyrolactone. Lit. b.p., 98° at 15 mm; η_{D} 1.4410 (48).

Anal. Calcd. for $\text{C}_7\text{H}_{12}\text{O}_2$: C, 65.64; H, 9.37.

Found: C, 62.09, 62.62; H, 8.28, 8.66.

5-Isopropyl-2-methoxytetrahydrofuran. Attempts to prepare this

compound by the sequence of steps indicated in Chart 1, equation (a) and (b) were not successful as indicated by the n.m.r. of the product.

The n.m.r. and elemental analysis of the intermediate ester, 3-carbomethoxy-5-isopropyl-2-methoxytetrahydrofuran did not correspond to the expected values.

Method III (unsuccessful).

Methyl 5-isopropyl-2-furoate was prepared according to a published procedure described by Colonge and Girantet (43).

Methyl 2-furoate (126 g, 1 mole) and aluminum chloride (200 g) were placed in 350 ml of dichloroethane and the mixture was cooled to 5°. Isopropyl bromide (123 g, 1.08 mole) was added dropwise over a period of 1 hour while the temperature was maintained at 5°. After the addition of the bromide, the mixture was allowed to come to room temperature and hydrogen bromide was evolved. After standing for 15 hours the mixture was added to 500 g of ice and extracted twice with dichloroethane. The combined extracts were washed first with a saturated aqueous solution of sodium chloride followed by an aqueous solution of sodium bicarbonate and then dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the solvent removed in a rotatory evaporator. The residual liquid was fractionated under reduced pressure and 120 g of material boiling between 85° and 125° at 15 mm was collected. The material was again fractionated using the spinning band column to give 64 g (38%) of a compound boiling at 92-94° at 8 mm; η_D^{23} , 1.4870. Lit. b.p., 91-93° at 8 mm; η_D^{25} , 1.4835 (43).

5-Isopropylfurfuryl alcohol was prepared according to the procedure by Colonge and Girantet (43).

Lithium aluminum hydride (12.92 g, 0.34 mole) was placed in 300 ml of anhydrous ether. Methyl 5-isopropyl-2-furoate (57 g, 0.34 mole) was added dropwise at such a rate that the ether refluxed gently.

After addition of the ester, the mixture was refluxed for about 2 hours. Excess hydride was destroyed by adding a 15% aqueous solution of potassium hydroxide to the mixture. The ether layer was decanted and the granular precipitate extracted with fresh refluxing ether. The combined ether layers were dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the ether removed via the rotatory evaporator. The residue was distilled under reduced pressure to give 38 g (73%) of material boiling at 98° at 12 mm; η_D^{23} , 1.4785. Lit. b.p., 97.5° at 12 mm; η_D^{25} , 1.4700 (43).

5-Isopropyltetrahydrofurfuryl alcohol was prepared according to a procedure described by Colonge and Girantet (44).

5-Isopropylfurfuryl alcohol (37 g, 0.24 mole) in 100 ml of ethanol was hydrogenated using Raney Nickel (6 g) as catalyst at 100° at 700 p.s.i. pressure for 12 hours. The catalyst was then removed and the ethanol evaporated using the rotatory evaporator. The residue was distilled under reduced pressure to give a compound (35 g, 92%) boiling at $93-94^{\circ}$ at 14 mm; η_D^{23} , 1.4505. Lit. b.p. 92° at 14 mm; η_D^{25} , 1.4495 (43).

Pyrolysis of 5-isopropyltetrahydrofurfuryl alcohol was done by modifying the procedure published by Colonge and Girantet (43).

The apparatus consisted of a quartz tube, 75 cm long with a diameter of 25 mm and equipped with standard joints at both ends. The tube was packed with neutral alumina and heated along its length by means

of heating tape. The temperature was maintained at 360-380°C. The alcohol was then added dropwise into the tube and the distillate was collected at the other end by means of a condenser and a dry ice-acetone cooled receiver. Extensive charring occurred during the addition of the alcohol. The distillate collected represented less than 10% yield and consisted of 3 major peaks on the gas liquid chromatograph. These were collected using the autoprep and their n.m.r. spectra clearly indicated that the expected product 6-isopropyl-2,3-dihdropyran had not been formed.

PART II. AUTHENTIC MIXED HYDRIDE REDUCTION PRODUCTS.

4-Alkoxy-1-butanol. The following general procedure (2) was used to prepare these compounds.

A mixture of equimolar amounts of 4-chloro-1-butanol and 3,4-dihdropyran containing a catalytic amount of p-toluenesulfonic acid was refluxed for two hours. The reaction mixture was then concentrated, diluted with water and extracted with ether. The ether extract was washed with an aqueous solution of sodium bicarbonate and then dried over anhydrous magnesium sulfate. Following the separation of the sulfate, the filtrate was freed from ether yielding crude 2-(4-chlorobutoxy)-tetrahydropyran. This crude product was mixed with the desired alcohol containing the appropriate amount of its sodium salt

and the mixture was stirred under reflux for 20 hours. The excess alcohol was removed and the residue hydrolysed by heating with 10% aqueous sulfuric acid under reflux overnight. The mixture darkened considerably during the reflux period. The mixture was extracted with chloroform and the chloroform extract washed with aqueous sodium bicarbonate, saturated aqueous sodium chloride and with water and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was distilled under reduced pressure. Only a few hundred milligrams of pure product were obtained in each case due to the extensive polymerization. Accordingly yields are not quoted below.

1. 4-Methoxy-1-butanol. B.p., 60° at 19 mm; η_D^{26} , 1.4194.
Lit. b.p., $59-63^{\circ}$ at 7 mm; η_D^{25} , 1.4189 (49).
2. 4-Ethoxy-1-butanol. B.p., 78° at 18 mm; η_D^{26} , 1.4201.
Lit. b.p., $83-84^{\circ}$ at 16 mm; η_D^{20} , 1.4229 (50).
3. 4-Isopropoxy-1-butanol. B.p., 87° at 15 mm; η_D^{24} , 1.4237.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.65; H, 12.11.

Found: C, 63.51; H, 12.09.

PART III. THE REDUCTION OF ACETALS WITH $LiAlH_4-AlCl_3$.

The same reduction procedure was employed for all of the acetals. A typical example is shown below. This procedure was described by Leggetter and Brown (1).

Reduction of 2-methoxytetrahydrofuran.

To a stirred mixture of 2-methoxytetrahydrofuran (5.0 g, 0.049 mole) and lithium aluminum hydride (1.86 g, 0.049 mole) in 50 ml of anhydrous diethyl ether, all at room temperature, was added a solution of aluminum chloride (6.47 g, 0.049 mole) in 50 ml of ether. An exothermic reaction occurred during the addition, hence this required a period of about 15 minutes. After the addition was complete, the mixture was stirred at room temperature for 2 hours. The resulting mixture was then cooled in ice and then treated cautiously with 7 ml of water followed by 7 ml of a 15% aqueous solution of potassium hydroxide. The inorganic material was removed by filtration and then extracted continuously with ether for 12 hours. This ether extract, combined with the original ether layer, was dried over anhydrous magnesium sulfate and then separated from the sulfate by filtration. The ether was removed by careful fractionation so that none of the product was distilled over. This was tested by taking gas liquid chromatograms of several portions of the distillate during the fractionation. When about 2/3 of the ether had been removed, the composition of the residue was determined by gas liquid chromatography. Finally the residue was distilled under reduced pressure to give 4.4 g (86%) of material boiling at 84-85° at 24 mm; n_D^{27} , 1.4184. Lit. b.p., 59-63° at 7 mm; n_D^{25} , 1.4189 (49). The infrared and nuclear magnetic resonance spectra of this material were identical with those of authentic 4-methoxy-1-butanol. The n.m.r.

spectra of authentic and reduction products are shown in Fig. 5 and Fig. 6 respectively.

Reduction of 2-ethoxytetrahydrofuran gave an 82% yield of 4-ethoxy-1-butanol. B.p., 83-84° at 17 mm; η_D^{26} , 1.4201. Lit. b.p., 83-84° at 16 mm; η_D^{20} , 1.4229 (50).

Reduction of 2-isopropoxytetrahydrofuran gave an 80% yield of 4-isopropoxy-1-butanol. B.p., 90-92° at 18 mm; η_D^{25} , 1.4215.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.65; H, 12.11.

Found: C, 63.44; H, 12.02.

Reduction of 2-t-butoxytetrahydrofuran gave an 86% yield of 4-t-butoxy-1-butanol boiling at 95-96° at 17 mm; η_D^{25} , 1.4253. Lit. b.p., 72-74° at 10 mm; η_D^{18} , 1.4301 (2).

Reduction of 2-methoxy-5-methoxymethyltetrahydrofuran gave an 84% yield of 1,5-dimethoxy-2-pentanol boiling at 95° at 42 mm; η_D^{23} , 1.4248.

Anal. Calcd. for $C_7H_{16}O_3$: C, 56.76 ; H, 10.81.

Found: C, 56.23, 56.58; H, 10.37, 10.34.

Reduction of 5-methoxy-5-methyltetrahydrofuran gave a 50% yield of 5-methoxy-2-pentanol boiling at 65° at 20 mm; η_D^{25} , 1.4220.

Anal. Calcd. for $C_6H_{12}O_2$: C, 61.01; H, 11.86.

Found: C, 60.65; H, 11.64.

The other product of reduction, 2-methyltetrahydrofuran was identified by comparison of its gas liquid chromatography retention time with that of commercially available material.

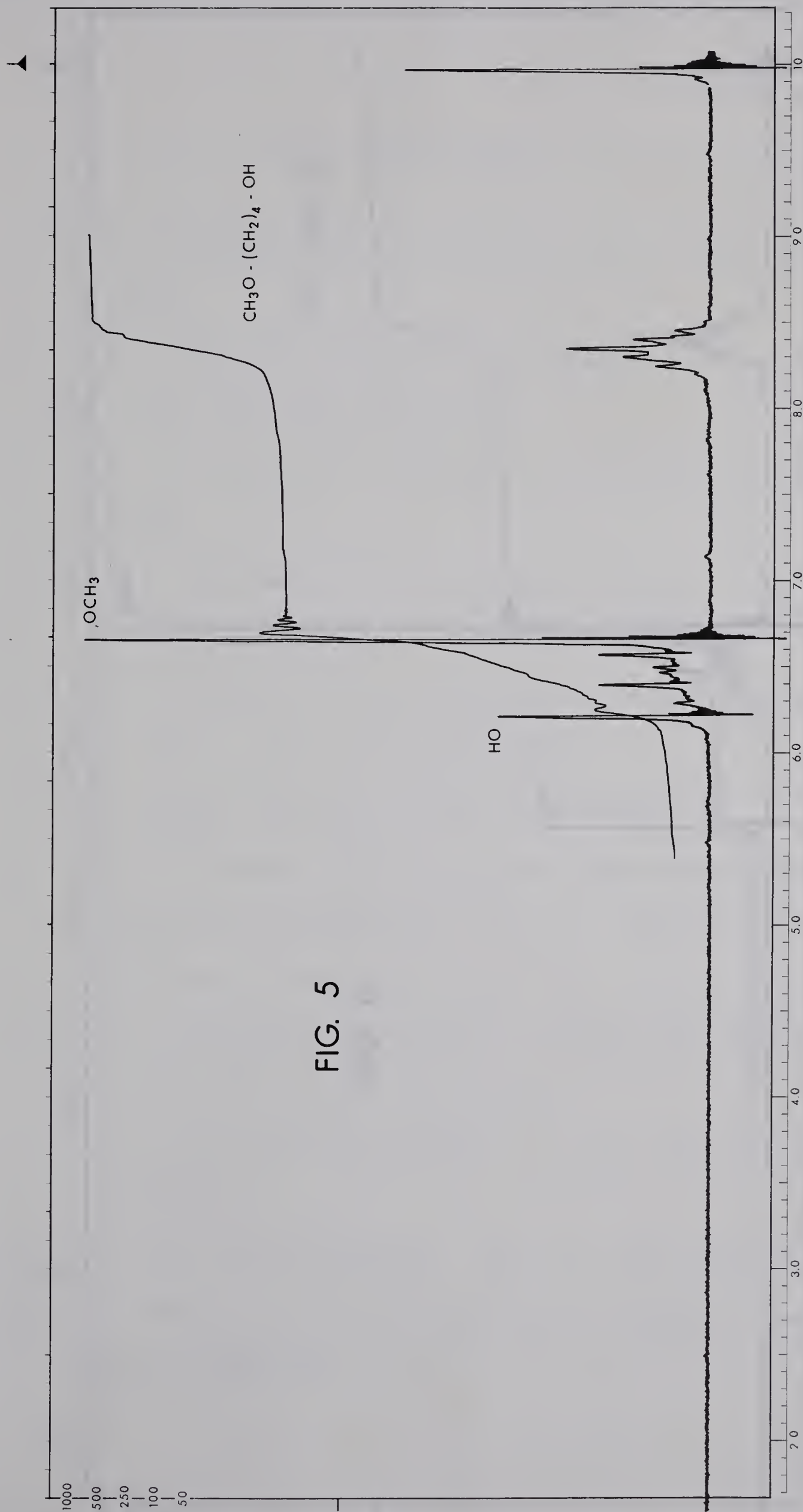


FIG. 5

N.M.R. spectrum of product from hydrogenolysis of 2-methoxytetrahydrofuran (no solvent).

(referred to tetramethylsilane)

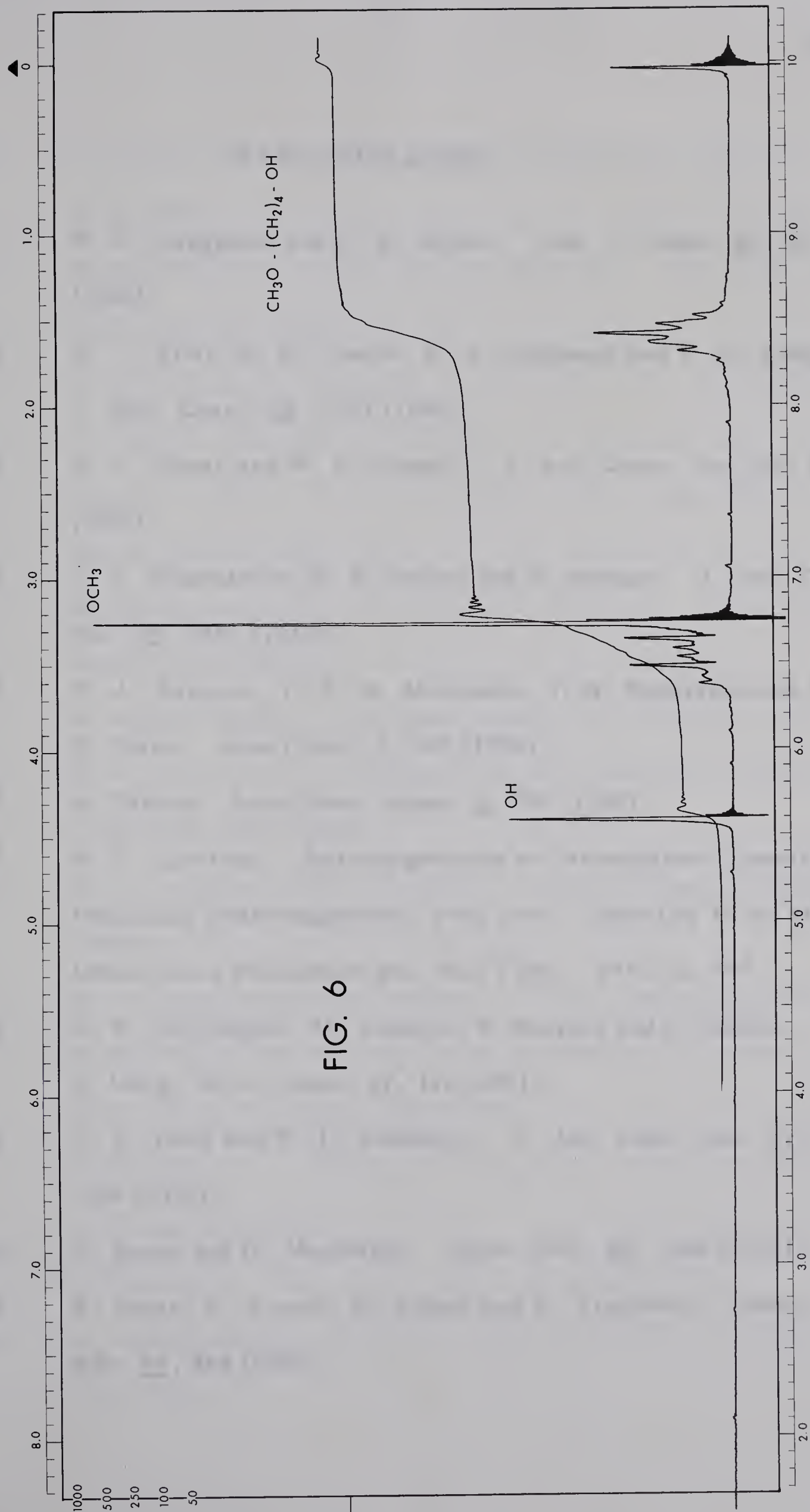


FIG. 6

N.M.R. spectrum of authentic 4-methoxy-1-butanol.

(solvent carbon tetrachloride) (referred to tetramethylsilane)

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